HTA Austria
Austrian Institute for
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Hepatic and portal vein embolisation prior to major hepatectomy

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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Content

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List of abbreviations

99mTc Technetium-99m (99mTc)
AASLD.....American Association for the Study of Liver Diseases
AE.....Adverse event
ALPPS.....Associating liver partition and portal vein ligation for staged hepatectomy
APASL .....The Asian Pacific Association For The Study of The Liver
BE.....Bi-embolisation
BMI .....Body mass index
CI.....Confidence interval
CT.....Computed-tomography
EASL.....European Association for the Study of the Liver
FLR.....Future liver remnant
FLR-F .....Future liver remnant function
FLR-V .....Future liver remnant volume
HCC .....Hepatocellular carcinoma
HPVE .....Hepatic and portal vein embolisation
HVE.....Hepatic vein embolisation
ICC.....Intrahepatic cholangiocarcinoma
ICG.....Indocyanine green
ICGR15 .....Indocyanine green retention in the liver after 15 minutes
INAHTA .....International Network of Agencies for Health Technology Assessment
IQR.....Interquartile range
LVD.....Liver venous deprivation
MHV.....Middle hepatic vein
NA .....Not applicable
NASH.....Non-alcoholic steatohepatitis
NBCA.....N-butyl cyanoacrylate
NE .....Not estimable
NR .....Not reported
NRCT.....Non-randomised controlled trial
PHLF .....Post-hepatectomy liver failure
PVA .....Polyvinyl alcohol
PVE .....Portal vein embolisation
RASPE .....Radiological simultaneous porto-hepatic vein embolisation
RCT.....Randomised controlled trial
RHV .....Right hepatic vein
RoB.....Risk of bias
SPECT-CT .....Single-photon emission computed tomography/computed tomography
TACE .....Transarterial chemoembolisation
TLV.....Total liver volume

Executive Summary

Introduction

Health Problem

Patients with primary hepatic or biliary tract malignancies, metastatic tumours of the liver, or benign tumours to the liver may require major hepatectomy as part of their treatment course. However, for many patients, major resection is initially unviable because the size and/or function of the part of the liver that would remain after surgery (the future liver remnant [FLR]) would put them at too great a risk of post-hepatectomy liver failure (PHLF).

Major-Leberresektion riskant aufgrund Größe/Funktion der künftigen Restleber

Description of Technology

Various techniques intended to increase the volume of the FLR (FLR-V) prior to major hepatectomy have been developed. Currently, portal vein embolisation (PVE) – a procedure in which blood flow to the tumour-bearing part of the liver is occluded – is the standard of care strategy for liver regeneration in many surgical departments. However, 20-30% of patients remain unsuitable for resection after PVE due mainly to either disease progression after embolisation or insufficient hypertrophy of the FLR. The intervention under investigation – hepatic and portal vein embolisation (HPVE) – seeks to occlude both portal inflow and hepatic venous outflow with the intent to accelerate hypertrophy of the FLR. A number of technical variations of HPVE have been described, including liver venous deprivation (LVD), bi- or double-embolisation, radiological simultaneous porto-hepatic vein embolisation (RASPE), and sequential PVE followed by hepatic vein embolisation (HVE).

Pfortaderembolisation (PVE) ist Standardversorgung, jedoch in 20-30 % folgende Resektion unmöglich;

Lebervenen- und Pfortaderembolisation (HPVE) soll Hypertrophie der Restleber beschleunigen

Methods

This report aimed to assess whether HPVE in comparison to PVE or other techniques intended to induce FLR hypertrophy prior to major hepatectomy is a more effective and safe procedure. To do so, a systematic literature review of the available evidence was conducted. Given the nature of the available data, the reporting of results was limited to a narrative review; no statistical analyses were undertaken.

HPVE im Vergleich zu PVE wirksamer/sicherer?

Domain effectiveness

The following outcomes were defined as *crucial* to derive a recommendation: life expectancy/overall survival, PHLF, rapid tumour growth due to PVE, ineligibility for planned resection due to disease progression, and ineligibility for planned resection due to insufficient hypertrophy.

entscheidungsrelevante Wirksamkeits-Endpunkte

Domain safety

The following safety outcomes were defined as *crucial* to derive a recommendation: postoperative mortality, morbidity (specifically, serious adverse events [AEs] and other reported hepatobiliary complications), and surgical- or device-related AEs.

entscheidungsrelevante Sicherheits-Endpunkte

Results

Available evidence

3 retrospektive Vergleichsstudien & 2 prospektive Fallserien eingeschlossen

A total of three retrospective comparative studies were eligible for inclusion to inform the assessment of the safety and effectiveness of HPVE vs PVE. Furthermore, two prospective case series were included to provide additional evidence on the safety of HPVE. No studies comparing HPVE to other comparator techniques were identified. Overall, the quality of evidence was low or very low.

Clinical effectiveness

Daten zum Krankheitsfortschritt nach Embolisation

No data were retrieved from the literature to inform the outcomes of life expectancy/overall survival and rapid tumour growth due to PVE. Data pertaining to disease progression after embolisation were reported in terms of patient ineligibility for planned resection – where ineligibility is due to disease progression, tumour growth due to PVE may have occurred.

Leberversagen nach Hepatektomie (PHLF)

PHLF was reported by two out of three comparative studies; one found a statistically significant difference in PHLF between patients who had undergone HPVE prior to hepatectomy in comparison to patients who had undergone PVE (HPVE 0% vs PVE 21.9%, p=0.012). The second study reported no instances of PHLF in either the HPVE or PVE groups.

Krankheitsfortschritt, unzureichende Restleber-Hypertrophie

Overall, patients unable to undergo resection due to disease progression after HPVE compared with PVE ranged from 0-13.5% vs 0-9.8%, respectively. Insufficient FLR hypertrophy (volume and function) was reported in 0-3.4% of patients after HPVE compared with 2.8-9.1% after PVE.

Safety

postoperative Mortalität

With regard to postoperative mortality, the 90-day mortality rate ranged between 0-12.2% and 3.1-6.5% among patients who had undergone HPVE and PVE, respectively, across the three comparative studies. In two of these studies, differences in 90-day mortality between HPVE and PVE groups were reported as not statistically significant. In the third, statistical significance was not reported. In the two case series, the postoperative mortality rate ranged from 10.0-11.1%.

operations- oder gerätebedingte unerwünschte Ereignisse

In the comparative studies, the rate of surgical- or device-related AEs after embolisation ranged from 5.4-20.7% and 2.4-13.6% in patients after HPVE and PVE, respectively. In the case series, they occurred in 8.3-16.6% of patients after HPVE. These included non-target embolisation, minor pre-hepatic haematoma, transient asthenia, bland thrombosis of the proximal right portal vein and high intraoperative portal pressure requiring associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). No major complications were reported in four of five studies. The fifth study reported two serious AEs (Clavien-Dindo grade ≥III) after embolisation. Both events occurred in the PVE group, although the difference between groups was not significant (p=not significant).

schwere unerwünschte Ereignisse

After hepatectomy, serious AEs (Clavien-Dindo grade ≥III) were reported in 3.7-20.0% of patients who had undergone preoperative HPVE and in 9.7-31.0% who had undergone PVE. Serious postoperative AEs occurred in 11.1% and 70% of patients across the two case series.

Additionally, one comparative study provided data on the following postoperative hepatobiliary complications: PHLF, biliary leak, ascites, intra-abdominal collection, and portal thrombosis. With the exception of PHLF, differences between groups with regards to the remaining outcomes were not statistically significant. A second comparative study provided data on a composite hepatobiliary complications outcome (comprising ascites, encephalopathy, jaundice or PHLF), finding a non-significant difference between groups.

postoperative unerwünschte Ereignisse

Upcoming evidence

In the search for upcoming evidence, two ongoing trials were identified that are due to be completed in 2022. One is a multi-centre randomised controlled trial (RCT) which will assess as its primary outcome the increase in FLR-V three weeks post-embolisation. The second trial comprises two parts – a non-comparative study to assess the safety and feasibility of HPVE (currently underway), which is planned to be followed by a subsequent RCT.

2 laufende Studien

Reimbursement

No information on the price or reimbursement status of the embolic materials used to occlude the portal or hepatic veins was accessible or provided by the manufacturers. The HPVE procedure itself is currently not reimbursed in Austria.

keine Kostenrückerstattung in Österreich

Discussion

The overall quality of evidence for the clinical effectiveness and safety of HPVE compared to comparator volume optimisation strategies is very low to low, precluding a recommendation at this time. Study design (three retrospective comparative studies and two small [n=12] case series) contributed to these poor quality ratings. Nonetheless, these studies provide preliminary evidence that FLR hypertrophy (an *important* but not *crucial* outcome) is greater with HPVE compared to PVE. Future research should distinguish between patients with hepatocellular carcinoma (HCC) and colorectal liver metastases as there may be differences in effectiveness between these patient groups. HCC typically occurs in cirrhotic or semi-cirrhotic livers with reduced capacity for liver regeneration. In contrast, colorectal liver metastases tend to occur in otherwise healthy livers for which procedures to induce hypertrophy are more likely to be successful.

keine Empfehlung von HPVE aufgrund der (sehr) niedrigen Qualität der Evidenz

künftige Studien: Unterscheidung zw. Leberzellenkarzinom und kolorektalen Lebermetastasen

Conclusion

High-quality evidence on the safety and effectiveness of HPVE in comparison to PVE is lacking. It is recommended a re-evaluation be undertaken in 2023 when evidence from the ongoing RCTs becomes available.

Neubewertung 2023 empfohlen

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

major hepatectomy in 75% of patients not possible due to risk of post-hepatectomy liver failure

Bei Patient*innen mit primärem Leber- oder Gallengangskrebs, metastasierenden Lebertumoren oder gutartigen Lebertumoren kann im Rahmen des Behandlungsverlaufs eine Major-Hepatektomie erforderlich sein. Die Major-Hepatektomie stellt einen chirurgischen Eingriff dar, welcher als Resektion von mindestens drei oder vier Lebersegmenten definiert ist. Jedoch ist bei vielen Patient*innen eine Major-Resektion zunächst nicht durchführbar, da die Größe und/oder Funktion des nach der Operation verbleibenden Leberteils (future liver remnant, FLR) ein zu großes Risiko für ein Leberversagen nach der Hepatektomie darstellt, welches mit hoher Morbidität und Mortalität verbunden ist. Zum Zeitpunkt der Diagnose gelten 75 % der Patient*innen mit einem primären oder sekundären Lebertumor als ungeeignet für eine Resektion.

incidences and mortality rates of liver and colorectal cancer in Austria

risk factors

In Österreich war Leberkrebs im Jahr 2020 die dreizehnthäufigste diagnostizierte Krebsart (1.114 Neuerkrankungen) und die sechsthäufigste krebsbedingte Todesursache (993 leberkrebsbedingte Todesfälle). Darmkrebs hingegen war die vierthäufigste diagnostizierte Krebsart (4.499 Neuerkrankungen) und die zweithäufigste krebsbedingte Todesursache (2.299 Todesfälle). Etwa 15-25 % der Darmkrebspatient*innen haben zum Zeitpunkt der Erstdiagnose bereits Lebermetastasen, während etwa 50 % der Patient*innen mit Darmkrebs im Laufe ihrer Erkrankung Lebermetastasen entwickeln. Die Inzidenz ist bei Männern etwas höher, und das Erkrankungsrisiko nimmt mit dem Alter zu.

Beschreibung der Technologie

portal vein embolisation as standard of care, but in 20-30% following resection unsuitable due to disease progression or insufficient hypertrophy

different variations of HPVE

Es wurden bereits verschiedene Techniken zur Vergrößerung des Volumens der Pfortader vor einer Major-Hepatektomie entwickelt. Derzeit ist die Pfortaderembolisation, ein Verfahren bei dem der Blutfluss zum tumortragenden Teil der Leber verschlossen wird, in vielen chirurgischen Abteilungen die Standardstrategie für die Leberregeneration. Allerdings sind 20-30 % der Patient*innen nach einer Pfortaderembolisation für eine Resektion nicht geeignet, hauptsächlich weil die Krankheit nach der Embolisation fortschreitet oder der FLR nicht ausreichend hypertrophiert ist. Der in dieser Übersichtsarbeit untersuchte Eingriff , die Leber- und Pfortaderembolisation (HPVE), zielt darauf ab, sowohl den portalen Zufluss als auch den hepatischen Venenabfluss zu verschließen, um die Hypertrophie des FLR zu beschleunigen. Es wurde eine Reihe technischer Varianten der HPVE beschrieben, darunter die Lebervenendeprivation (LVD), die Bi- oder Doppelembolisation, die radiologische simultane porto-hepatische Venenembolisation (RASPE) und die Pfortader- und Lebervenenembolisation.

Methoden

HPVE more effective/safer compared to portal vein embolisation?

In diesem Bericht wird untersucht, ob die HPVE wirksamer und sicherer ist als Pfortaderembolisation oder anderen Techniken zur Induktion einer FLR-Hypertrophie vor einer Major-Hepatektomie. Zu diesem Zweck wurde eine systematische Literatursuche in vier Datenbanken sowie eine Handsuche durchgeführt. Insgesamt wurden 808 Zitate ermittelt.

data analysis and synthesis

Die Daten aus den fünf ausgewählten Studien wurden von einer Wissenschafterin systematisch in Datenextraktionstabellen extrahiert, mit Überprüfung durch einen zweiten Wissenschafter. Weiters wurden die Studien von zwei unabhängigen Forscher*innen systematisch auf ihre interne Validität und das Verzerrungsrisiko geprüft. Die Daten zu den patient*innenrelevanten Endpunkten 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.

risk of bias and quality of evidence

Klinische Wirksamkeit

crucial outcomes: effectiveness and …

Die folgenden patient*innenrelevanten Endpunkte wurden als entscheidend für die Ableitung einer Empfehlung definiert: Lebenserwartung/Gesamtüberleben, Leberversagen nach der Hepatektomie, schnelles Tumorwachstum aufgrund von Pfortaderembolisation, Untauglichkeit für eine geplante Resektion aufgrund von Krankheitsprogression bzw. aufgrund von unzureichender Hypertrophie.

Sicherheit

… safety

Die folgenden Sicherheitsergebnisse wurden als entscheidend für die Ableitung einer Empfehlung definiert: postoperative Mortalität, Morbidität (insbesondere schwerwiegende unerwünschte Ereignisse und andere hepatobiliäre Komplikationen) und chirurgische oder gerätebezogene unerwünschte Ereignisse.

Ergebnisse

Verfügbare Evidenz

3 retrospective comparative studies and 2 prospective case series with (very) low quality of evidence

Insgesamt wurden drei retrospektive Vergleichsstudien eingeschlossen, um die Sicherheit und Wirksamkeit von HPVE gegenüber Pfortaderembolisation zu bewerten. Darüber hinaus wurden zusätzlich zwei prospektive Fallserien eingeschlossen, um weitere Evidenz hinsichtlich der Sicherheit von HPVE zu liefern. Es wurden keine Studien identifiziert, welche HPVE mit anderen Vergleichstechniken verglichen. Die Qualität der Evidenz war insgesamt (sehr) gering.

Klinische Wirksamkeit

life expectancy/overall survival and rapid tumour growth: no evidence

Aus der Literatur konnten keine Daten zu den Endpunkten Lebenserwartung/Gesamtüberleben und schnelles Tumorwachstum aufgrund von Pfortaderembolisation entnommen werden. Daten über den Krankheitsfortschritt nach der Embolisation wurden hinsichtlich der Untauglichkeit der Patient*innen für eine geplante Resektion berichtet. Wenn die Untauglichkeit auf den Krankheitsfortschritt zurückzuführen war, hat ein Tumorwachstum möglicherweise aufgrund der Pfortaderembolisation stattgefunden.

post-hepatectomy liver failure: statistically significant (s.s.) difference (1/3 studies)

In zwei von drei Vergleichsstudien wurde ein Leberversagen nach der Hepatektomie berichtet. Davon wurde in der einen Studie ein statistisch signifikanter Unterschied hinsichtlich eines Leberversagens nach der Hepatektomie zwischen Patient*innen, welche sich vor der Hepatektomie einer HPVE vs. einer Pfortaderembolisation unterzogen haben, festgestellt (HPVE 0 % vs. Pfortaderembolisation 21,9 %, p=0,012). In der zweiten Studie wurden weder

in der HPVE- noch in der Pfortaderembolisations-Gruppe Fälle von Leberversagen nach der Hepatektomie gemeldet. Die Ergebnisse der dritten Studie waren nicht bewertbar.

unable to undergo resection due to disease progression or insufficient FLR hypertrophy

Insgesamt lag die Zahl der Patient*innen, bei denen eine Resektion aufgrund des Fortschreitens der Erkrankung nicht möglich war, zwischen 0-13,5 % (HPVE) bzw. 0-9,8 % (Pfortaderembolisation). Eine unzureichende FLR-Hypertrophie (Volumen und Funktion) wurde bei 0-3,4 % der Patient*innen nach einer HPVE im Vergleich zu 2,8-9,1 % nach einer Pfortaderembolisation festgestellt.

Sicherheit

postoperative mortality: not s.s. difference (2/3 studies)

Was die postoperative Mortalität anbelangt, so lag die 90-Tage-Mortalität bei den Patient*innen, welche sich einer HPVE bzw. Pfortaderembolisation unterzogen haben, in den drei Vergleichsstudien zwischen 0-12,2 % und 3,1-6,5 %. In zwei dieser Studien wurde der Gruppenunterschiede (HPVE vs. Pfortaderembolisation) in der 90-Tage- Mortalität als statistisch nicht signifikant angegeben. In der dritten Studie wurde statistische Signifikanz nicht berichtet. In den beiden Fallserien lag die postoperative Mortalitätsrate zwischen 10,0 und 11,1 %.

surgical- or device-related adverse events (5/5 studies)

In den Vergleichsstudien lag die Rate der chirurgischen oder gerätebedingten Nebenwirkungen nach der Embolisation zwischen 5,4-20,7 % (HPVE) und 2,4-13,6 % (Pfortaderembolisation). In den Fallserien traten sie bei 8,3-16,6 % der Patient*innen nach HPVE auf. Folgende unerwünschte Ereignisse wurden genannt: nicht zielgerichtete Embolisation, geringfügiges prähepatisches Hämatom, vorübergehende Asthenie, blande Thrombose der proximalen rechten Pfortader und hoher intraoperativer Pfortaderdruck, welcher ein zweizeitiges Verfahren zur Resektion von initial inoperablen Lebertumoren (Associating Liver Partition with Portal vein ligation for Staged hepatectomy, ALPPS) erforderlich machte.

major complications (1/5 studies)

In vier von fünf Studien wurden keine schwerwiegenden Komplikationen gemeldet. In der fünften Studie wurden zwei schwerwiegende unerwünschte Ereignisse (Clavien-Dindo-Grad ≥III) nach der Embolisation gemeldet. Beide Ereignisse traten in der Pfortaderembolisations-Gruppe auf, obwohl der Unterschied zwischen den Gruppen nicht signifikant war.

serious adverse events (5/5 studies)

Nach der Hepatektomie wurden bei 3,7-20,0 % der Patient*innen, die sich einer präoperativen HPVE unterzogen haben, und bei 9,7-31,0 % der Patient*innen, die sich einer Pfortaderembolisation unterzogen haben, schwerwiegende unerwünschte Ereignisse (Clavien-Dindo-Grad ≥III) gemeldet. Schwerwiegende postoperative unerwünschte Ereignisse traten in den beiden Fallserien in 11,1 % bzw. 70 % der Patient*innen auf.

postoperative complications: no s.s. difference (except liver failure) (2/2 studies)

Darüber hinaus lieferte eine Vergleichsstudie Daten zu den folgenden postoperativen hepatobiliären Komplikationen: Leberversagen nach der Hepatektomie, biliäres Leck, Bauchwassersucht (Aszites), intraabdominale Ansammlung und Pfortaderthrombose. Mit Ausnahme von Leberversagen nach der Hepatektomie waren die Unterschiede zwischen den Gruppen in Bezug auf die übrigen Ergebnisse statistisch nicht signifikant. Eine zweite Vergleichsstudie lieferte Daten zu hepatobiliären Komplikationen (bestehend aus Aszites, Enzephalopathie, Gelbsucht oder Leberversagen nach der Hepatektomie), wobei ein nicht signifikanter Unterschied zwischen den Gruppen festgestellt wurde.

Laufende Studien

2 ongoing studies

Bei der Suche nach künftiger Evidenz wurden zwei laufende Studien ermittelt, welche im Jahr 2022 abgeschlossen werden sollen. Bei der einen handelt es sich um eine multizentrische randomisierte kontrollierte Studie (RCT), die als primäres Ergebnis den Anstieg des Volumes der FLR drei Wochen nach der Embolisation bewerten wird. Die zweite Studie besteht aus zwei Teilen: eine nicht vergleichende Studie zur Bewertung der Sicherheit und Durchführbarkeit von HPVE (derzeit im Gange), an welche sich eine weitere RCT anschließen soll.

Kostenerstattung

no reimburesement of HPVE in Austria

Es waren keine Informationen über den Preis oder den Erstattungsstatus der Emboliematerialien, welche zum Verschluss der Pfortader oder der Lebervenen verwendet werden, zugänglich oder wurden von den Herstellern zur Verfügung gestellt. Das HPVE-Verfahren selbst wird in Österreich derzeit nicht erstattet.

Diskussion

no recommendation of HPVE due to (very) low quality of evidence

Die Gesamtqualität der Evidenz für die klinische Wirksamkeit und Sicherheit von HPVE im Vergleich zu vergleichbaren Strategien zur Volumenoptimierung ist (sehr) gering, was eine Empfehlung zum jetzigen Zeitpunkt ausschließt. Das Studiendesign (drei retrospektive Vergleichsstudien und zwei kleine [n=12] Fallserien) hat zu diesen schlechten Qualitätsbewertungen beigetragen. Nichtsdestotrotz liefern diese Studien vorläufige Beweise dafür, dass die FLR-Hypertrophie (ein wichtiges, aber nicht entscheidendes Ergebnis) bei HPVE im Vergleich zu Pfortaderembolisation größer ist.

future studies: differentiation between hepatocellular carcinoma and colorectal liver metastases

Bei künftigen Untersuchungen sollte zwischen Patient*innen mit Leberzellenkarzinom und kolorektalen Lebermetastasen unterschieden werden, da es möglicherweise Unterschiede in der Wirksamkeit zwischen diesen Patient*innengruppen gibt. Leberzellenkarzinom tritt typischerweise in zirrhotischen oder halbzirrhotischen Lebern auf, in denen die Fähigkeit zur Leberregeneration eingeschränkt ist. Im Gegensatz dazu treten kolorektale Lebermetastasen in der Regel in ansonsten gesunden Lebern auf, bei denen Verfahren zur Induktion von Hypertrophie eher erfolgreich sind.

Empfehlung

limited internal and external validity

Die vorliegende Evidenz ist unzureichend und mit begrenzter interner und externer Validität, um den klinischen Nutzen von HPVE im Vergleich zu Pfortaderembolisation bei Patient*innen, welche sich einer Major-Leberresektion unterziehen, zu bewerten.

(very) low quality of evidence

Aufgrund dieser insgesamt (sehr) geringen Evidenzstärke können keine endgültigen Schlussfolgerungen zur vergleichenden Wirksamkeit von HPVE gezogen werden. Es fehlen weitere Ergebnisse aus gut konzipierten RCTs, und die Ergebnisse laufender Studien sind abzuwarten. Künftige Forschung sollte sich auf mehr hochwertige RCTs mit umfassender Sicherheitsberichterstattung konzentrieren.

re-evaluation 2023 recommended

Es wird empfohlen, im Jahr 2023 eine Neubewertung vorzunehmen, wenn die Erkenntnisse aus den laufenden RCTs vorliegen.

1 Background

1.1 Overview of the disease, health condition and target population[1]

Hepatic and portal vein embolisation (HPVE) is a new technique intended to increase the volume of the future liver remnant (FLR) prior to major hepatectomy for patients in whom resection would otherwise be unviable.[2]

Lebervenen- und Pfortaderembolisation (HPVE) *vor* Major-Leberresektion, …

Indications for major hepatectomy[3]

Major hepatectomy is a surgical procedure defined as the resection of at least three or four liver segments [1, 2]. The common indications are [3-6]:

… die Entfernung von ≥3 Lebersegmenten

häufigsten Indikationen

- primary hepatic malignancy such as hepatocellular carcinoma (HCC) or biliary tract malignancy, including cholangiocarcinoma
- secondary metastases such as metastatic colorectal cancer
- benign primary liver tumours, including giant hemangiomas and adenomas.

Worldwide, liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death [7, 8]. In Europe, it was the thirteenth most diagnosed cancer and the seventh leading cause of cancer-related death in 2020 [8]. In Austria, there were 1,025 new cases of liver cancer in 2019 (accounting for approximately 2.5% of annual cancer cases), and although the disease is relatively rare, due to its poor prognosis, it was one of the thirteen most common causes of cancer-related death (867 liver-cancer related deaths; 4.2% of all cancer deaths) [9]. Men accounted for about three quarters of the annual numbers of new cases and of deaths from liver tumours (706 new cases and 630 deaths in Austria in 2019 were in men) [9].

Leberkrebs: häufig diagnostizierte Krebsform mit hoher Todesrate

Colorectal cancer was the second most diagnosed cancer and the second most common cause of cancer-related death in Europe in 2020, with nearly 520,000 new cases and 245,000 deaths [8, 10]. In Austria, it was the fourth most diagnosed cancer and the second most common cause of cancer-related death (4,499 new cases and 2,299 deaths in 2020) [8]. Its incidence is slightly higher in men, and the risk of the disease increases with age [10-12].[4] In Austria in 2019, 2,534 colorectal cancer diagnoses were made in men compared with 1,910 in women [13]. Approximately 15-25% of colorectal cancer patients will already have liver metastases at the time of the primary diagnosis [14], while about 50% of patients with colorectal cancer will develop liver metastases over the course of their disease [15]. Between 2017-2019, 16.2% of diagnoses of colorectal cancer made in Austria were not made until the tumour had disseminated beyond the locoregional area [13].

Darmkrebs: noch häufiger diagnostiziert mit noch höherer Todesrate

in 50 % der Patient*innen Lebermetastasen

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[1] This section addresses the EUnetHTA Core Model® domain CUR

[2] **A0001** – For which health conditions, and for what purposes is the technology used?

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

[4] **A0005** – What is the burden of disease for patients with the disease or health condition?
A0006 – What are the consequences of the disease or health condition for the society?

in 75 % der Lebertumorpatient*innen Resektion unmöglich (inoperabel)

At the time of diagnosis, 75% of patients with a primary or secondary liver tumour are considered unsuitable for resection because of insufficient size and/or function of the FLR. An insufficient FLR increases the risk of post-hepatectomy liver failure (PHLF), which is associated with high rates of morbidity and mortality [7, 16-18].[5]

in 5-20 % der Fälle Leberversagen nach Hepatektomie (PHLF); Risikofaktoren

The incidence of PHLF can increase from about 5% in patients with a healthy liver to upwards of 20% in patients with chronic liver disease [19]. Numerous factors may promote PHLF, such as preexisting portal hypertension, diabetes, obesity, chemotherapy, age >65 years old, size of the resection, and gender [18-20].[6]

Target population

präoperative Vergrößerung des kontralateralen Leberlappens

The target population comprises patients who require preoperative augmentation of contralateral liver lobes for resection to be considered viable, as well as patients who did not achieve adequate hepatic hypertrophy after either portal vein embolisation (PVE) or hepatic vein embolisation (HVE).[7]

keine standardisierten Grenzwerte

There are no standardised cut-offs to define the safe limits for major hepatectomy. To ensure the feasibility of resection, various factors are taken into account, including the patient's baseline liver function and the volume of the FLR (FLR-V) [19, 21]. Given these complexities, the size of the target population could not be estimated reliably via an epidemiological approach.[8] According to the submitting hospital about 50 HPVE procedures are performed annually.[9, 10]

preoperative volumetrische Auswertung

Preoperative volumetric evaluation (i.e. tumour volume, FLR-V and total liver volume [TLV]) can be assessed through a scintigraphy, an ultrasound, a computed tomography scan or magnetic resonance imaging [19, 22]. Some of these analyses can be coupled with three-dimensional reconstruction software to provide further information on tumour extent and vascular and biliary anatomy.

Volumen der künftigen Restleber: min. 20 % der gesunden Leber

The minimum FLR-V required for resection to be considered viable differs depending upon the function and underlying disease status of the liver [19]. In patients with a healthy liver, a minimum limit for the FLR of at least 20% of the volume of the healthy liver is recommended.

weitere Einflussfaktoren

The safe FLR limit is higher for patients with mild steatosis, cholestasis and early cirrhosis (Child's-Pugh A) (FLR of 30-35%) and for patients with severe steatosis and cholestasis (FLR of 40%) [19, 23]. A reduced liver function is often found in patients who have previously undergone chemotherapy, and this should also be considered when undertaking liver assessments prior to resection.[11]

Messung der Funktionalität der Leber

Functional liver assessment can be done by calculating indocyanine green (ICG) retention in the liver after 15 minutes (ICGR15) with an ICG clearance test. An ICGR15 above 15-20% is indicative of impaired hepatic functional reserve and is typically considered an indication for volume optimisation strate-

[5] **A0004** – What is the natural course of the disease or health condition?

[6] **A0003** – What are the known risk factors for the disease or health condition?

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

[8] **A0023** – How many people belong to the target population?

[9] **A0011** – How much are the technologies utilised?

[10] Source: information from the submitting hospital, 25.02.2022

[11] Prof Guy Maddern (The Queen Elizabeth Hospital, University of Adelaide Surgery Department, Australia), personal communication, 21.02.2022

gies [19, 24]. FLR function (FLR-F) can be assessed by 99mTc-mebrofenin hepatobiliary scintigraphy; a 99mTc-mebrofenin uptake rate <2.7%/min/m^2 is a predictor of PHLF and indicates a need for volume optimisation before resection [25].[12]

relevante ICD-10 Codes

The most relevant International Classification of Disease (ICD)-10 codes for this application are:

- K71 – Toxic liver disease
- K72 – Hepatic failure, not elsewhere classified
- K74 – Fibrosis and cirrhosis of liver
- K76 – Other diseases of liver
- K77 – Liver disorders in diseases classified elsewhere
- C7A – Malignant neuroendocrine tumours
- C7B.02 – Secondary neuroendocrine tumours of liver
- C17 – Malignant neoplasm of small intestine
- C18 – Malignant neoplasm of colon
- C19 – Malignant neoplasm of rectosigmoid junction
- C20 – Malignant neoplasm of rectum
- C22 – Malignant neoplasm of liver and intrahepatic bile ducts
- C23 – Malignant neoplasm of gallbladder
- C24 – Malignant neoplasm of other and unspecified parts of biliary tract
- E34.1 – Other hypersecretion of intestinal hormones.

1.2 Current clinical practice[1]

Techniken, damit Major-Leberresektion möglich; Standardbehandlung: Pfortaderembolisation (PVE)

To enable more patients to be eligible for major hepatectomy, various techniques have been developed, including PVE, radioembolisation, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), transarterial embolisation, and portal vein ligation. According to the peer-reviewed literature, PVE is the standard strategy used by many surgery departments to increase the FLR-V prior to major hepatectomy [24, 26, 27].[13]

Expertenkonsens zu PVE

A number of peer-reviewed literature sources – including expert consensus statements on the pretreatment assessment of hepatocellular carcinoma (2010) and the oncosurgery approach to managing liver metastases from colorectal cancer (2012) [15, 28] – provide guidance on the use of PVE as a liver regeneration strategy prior to major hepatectomy. PVE is commonly indicated if FLR-V represents <20-25% of the total volume of a healthy liver, <30-35% of a liver with mild steatosis, cholestasis and early cirrhosis (Child'sPugh A) or <40% of a liver with severe steatosis and cholestasis and in patients who have had extensive chemotherapy [15, 19, 24, 28, 29]. Contraindications for PVE are severe portal hypertension, uncontrollable intrahepatic portal to he-

Kontraindikationen

[12] **A0024** – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

[13] **A0025** – How is the disease or health condition currently managed according to published guidelines and in practice?

patic vein shunts, tumour thrombus in the portal vein and occlusion of the portal vein in FLR, portal vein tumour invasion, uncorrectable coagulopathy, tumour precluding safe transhepatic access, non-corrected biliary dilation and cholestasis, and renal failure [7, 26, 30, 31].

A targeted guidelines search for PVE was conducted on the 10th of March 2022 in Turning Research Into Practice (TRIP) Database, Guideline Central and Google.

klinische Praxisleitlinie zu PVE

The National Comprehensive Cancer Network's Clinical Practice Guidelines for hepatobiliary cancer (2021) [32] suggest PVE should be considered for patients with an estimated FLR/TLV ratio below recommended values who are otherwise suitable candidates for resection. European clinical practice guidelines describing PVE were not identified. However, current indications for liver surgery, according to EASL, AASLD and APASL guidelines, mentioned PVE (in combination or not with TACE) as a means to reduce the risk of hepatic failure [33]. PVE was also mentioned in two other guidelines [34, 35]and one guidance document [36], but no specific recommendations about the technique were made. The Australian consensus statement for the management of hepatocellular carcinoma did not mention PVE [37].

Durchführung der PVE: offene oder perkutane Operation

PVE can be performed by an open surgical transileocolic or percutaneous transhepatic approach. The latter can be performed through an ipsilateral or controlateral access route using ultrasonography and fluoroscopic guidance [7, 23]. The choice of the access route is based upon clinical and technical considerations, as well as the experience of the operator with one technique or another [30].

Einflussfaktoren des Ergebnisses

Various factors influence PVE outcomes, such as age, diabetes mellitus, and previous chemotherapy [38]. Moreover, chronically diseased livers will have an impaired capacity for liver regeneration [7, 38, 39].

versch. Materialien für Gefäßverschluss verwendet

A broad spectrum of embolic materials is available to achieve embolisation, including gelatin sponges, polyvinyl alcohol (PVA) particles, microspheres, N-butyl cyanoacrylate (NBCA), fibrin glue, absolute ethanol, sodium tetradecyl sulfate foam, with or without combination with coils or vascular plugs [7, 24, 29]. There is no consensus regarding a standard embolic agent to be used, although the access route influences the choice of the embolic material [30].

wenig schwere Komplikationen bei PVE

Major PVE complications are low (2-9%) and include vascular injury, biloma, infection, non-target embolisation, portal/mesenteric venous thrombosis and portal hypertension [7, 39, 40].

max. Volumen der künftigen Restleber nach 6 Wochen

A rapid FLR growth usually occurs in the first three to four weeks after PVE with a maximal volume reached by six weeks, allowing for hepatectomy four to six weeks after embolisation [7]. However, 20-30% of patients remain unsuitable for resection after PVE, mainly because of disease progression or insufficient hypertrophy (0.6-3.6%) [7, 19, 22, 39-43].

1.3 Features of the intervention[14]

HPVE: versch. Techniken, um Pfortaderzufluss *und* Lebervenenabfluss zu verschließen

The intervention under investigation is hepatic and portal vein embolisation (HPVE). This term encompasses a number of techniques, all of which are technical variations of one another. In essence, these procedures aim to occlude both the portal inflow and hepatic venous outflow, inducing more damage to the embolised liver compared with PVE alone to accelerate regeneration of the FLR.[15]

Lebervenendeprivation (erste Variante der simultanen HPVE): perkutanes Verfahren mit ihren Vorteilen

The first described variation of simultaneous HPVE was liver venous deprivation (LVD), which is a percutaneous procedure aiming to simultaneously block both portal inflow and hepatic venous outflow. This preoperative procedure may reduce the proportion of patients unable to undergo resection after embolisation due either to an insufficient FLR or tumour progression [26, 44]. Furthermore, this technique may allow patients at high risk of PVE failures, such as patients with a small FLR-V, extrahepatic biliary cancer (perihilar cancer and gallbladder cancer) and underlying liver injury to undergo resection. The development of LVD was also intended to counter the high complication rate of ALPPS whilst maintaining a fast FLR growth rate [6, 27]. Bi- or double-embolisation and radiological simultaneous porto-hepatic vein embolisation (RASPE) are both technical variations of LVD [45, 46].

sequentielle Abfolge möglich

HPVE can also be realised sequentially, with HVE being performed one to three weeks after PVE for patients whose FLR-V does not increase sufficiently after PVE alone [40].

HPVE = sequentielles und simultanes Verfahren

All technical variations of the simultaneous procedure, as well as sequential PVE and HVE are considered in this report. For simplicity, a single term – HPVE – has been used throughout the report.

HPVE-Verfahren im Detail

The HPVE procedure is usually carried out as follows: PVE is performed via a transhepatic percutaneous approach, followed by the embolisation of the hepatic vein circulation through a transjugular or transhepatic approach [40]. It is performed under local or general anaesthetic by an interventional radiologist [45, 47-49].[16] The combined HPVE procedure requires between one to five days hospital stay, with a median of three days [50, 51].

HPVE als Weiterentwicklung, um Hypertrophie der künftigen Restleber zu induzieren

HPVE is an evolution of existing techniques developed to induce FLR hypertrophy prior to major hepatectomy. Various materials can be used to occlude either the portal or hepatic vein, the majority of which have a CE marking.[17] The materials used for hepatic vein obstruction are either Amplatzer plug alone or Amplatzer plug with glue or coil [40, 51]. The vascular plug is larger (80-100%) than the selected hepatic vein [7]. This is in addition to the material used to occlude the portal vein. The embolic agents used for PVE were described previously in chapter 1.2.

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[14] This section addressed the EUnetHTA Core Model® domain TEC

[15] **B0001** – What is the technology and the comparator(s)?
B0002 – What is the claimed benefit of the technology in relation to the comparators?

[16] **B0004** – Who administers the technology and the comparators and in what context and level of care are they provided?

[17] **A0020** – For which indications has the technology received marketing authorisation or CE marking?
B0003 – What is the phase of development and implementation of the technology and the comparator(s)?

zusätzliche Hilfsmittel

Additional supplies required to complete the embolisation(s) include a catheter (e.g. microcatheter, flush catheter, transhepatic chlangiography catheter, Cobra shape catheter, 180° reverse-curve catheter for ipsilateral access), introducers or vascular sheaths, material to measure portal pressure as well as supplies to facilitate fluoroscopic and/or ultrasound guidance [24, 52]. The need for further supplies depends on the embolic agent(s) used. For example, when cyanoacrylate is used, syringes are needed for cyanoacrylate injection and for flushing [53]. PVE requires a digital subtraction angiography (DSA) suite [53].[18] Moreover, HPVE procedure requires equipment commonly found in an interventional radiological suite[19], including but not limited to a permanent, mounted, C-arm fluoroscopy unit capable of complex, multiobliquity imaging in the room with immediate access to a modern colour duplex ultrasound machine and a computed tomography (CT) scanner in certain case scenarios, monitoring and resuscitation equipment, power injectors for contrast administration, equipment for radiation monitoring and management [54, 55].

keine Kostenrückerstattung für HPVE in Österreich

There is no reference code in the Austrian catalogue of benefits (LKF, leistungsorientierte Krankenanstaltenfinanzierung) for the specific investigated intervention, HPVE, available. However, a reference code for the following hemihepatectomy (HL050) and other liver surgeries (HL079) exists and can therefore be reimbursed. No information on the price or reimbursement status of the embolic materials used to occlude the portal or hepatic veins was accessible or provided by the manufacturers.[20]

[18] **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)?

[19] Professor Guy Maddern (The Queen Elizabeth Hospital, University of Adelaide Surgery Department, Australia), personal communication, 15.03.2022

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

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is HPVE in comparison to PVE or other comparator volume optimisation strategies in patients undergoing major hepatectomy more effective and safe concerning PHLF, eligibility for planned resection, 30- or 90-day mortality, and surgically-related and major adverse events (AEs)?

PVE (Standardbehandlung) als Komparator

NB: The PICO criteria included multiple comparators, however, PVE was the only procedure used as a comparator in the available literature. PVE is the current standard strategy for hepatic hypertrophy prior to major resection.

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 undergoing major hepatectomy (open or laparoscopic) who require preoperative augmentation of contralateral liver lobes (hepatic hypertrophy) for resection to be considered viable OR Patients who did not achieve adequate hepatic hypertrophy following PVE or HVE. **Note:** Major hepatectomy is defined as the resection of at least three of four liver segments [1, 2]. The requirement for hypertrophy is defined as follows: where resection will leave insufficient hepatic reserve. A minimum FLR of 20-25% the volume of an otherwise healthy liver is required. For patients with chronic liver disease, the minimum required FLR-V is 30-50% [19, 56]. Expert advice is that hepatic reserve should represent 25% of the normal liver function (which mean a larger % is required if the liver is operating below normal levels). **ICD-10 codes:** K71, K72, K74, K76, and K77 C7A, C7B.02, C17,to C20, and C22 to C24 E34.1 **MeSH-terms:** hepatectomy **Rationale:** The population is derived from information provided by the submitting hospital, peer-reviewed literature [30, 39], and from discussion with a clinical expert.
Intervention	HPVE, including simultaneous HPVE and sequential PVE-HVE **MeSH-terms:** hepatic veins, portal vein, embolisation therapeutic, hepatectomy **Rationale:** The intervention is derived from information provided by the submitting hospital
Control	■ PVE ■ Portal vein ligation ■ ALPPS ■ Transarterial embolisation ■ Radioembolisation **MeSH-terms:** portal vein, embolisation therapeutic, hepatectomy **Rationale:** The comparators were derived from peer-reviewed literature [19, 30, 57], and discussions with the clinical expert.

Outcomes	
Efficacy	**Crucial outcomes:** ■ Life expectancy/overall survival ■ Liver failure ■ Rapid tumour growth due to PVE ■ Ineligibility for planned resection (including due to disease progression or insufficient hypertrophy) **Important clinical outcomes:** ■ % of hypertrophy/liver regeneration after HVE and PVE ■ Residual liver volume ■ Ratio of FLR to TLV ■ R0 resection rate ■ Tumour progression ■ Length of hospital stay **Rationale:** The outcomes were derived from peer-reviewed literature identified in the scoping phase, and discussion with the clinical expert.
Safety	All AEs and serious AEs, including: ■ 30- or 90- day mortality ■ Morbidity (e.g. poorly functioning remnant liver, liver failure, transaminase levels, ascites, and wound breakdown) ■ Surgical or device-related AEs (e.g. haemobilia and biliary leak, pneumothorax and/or haemothorax, arterial injuries, haemorrhage, cholangitis, liver abscess, hepatic infarction, non-target embolisation and portal vein thrombosis, recanalisation, and portal hypertension) ■ Withdrawal due to treatment-related AEs ■ Recovery time before being able to do the resection **Rationale:** The outcomes were derived from peer-reviewed literature identified in the scoping phase, and discussion with the clinical expert.
Study design	
Efficacy	■ Randomised controlled trials (RCTs) ■ Prospective and retrospective non-randomised controlled trials (NRCTs) ■ In the absence of comparative evidence, prospective case series will be included **Excluded:** narrative reviews, letters to the editor, author response, case reports, retrospective case series, conference abstracts
Safety	■ RCTs ■ Prospective and retrospective NRCTs ■ Prospective case-series **Excluded:** narrative reviews, letter to the editor, author response, case reports, retrospective case series, and conference abstracts. Retrospective NRCTs in which critical concerns about RoB were identified were also excluded.

Abbreviations: ALPPS – Associating Liver Partition and Portal vein Ligation for Staged hepatectomy, FLR – future liver remnant, FLR-F – function of the future liver remnant, FLR-V – volume of the future liver remnant, HPVE – hepatic and portal vein embolisation, NRCT – non-randomised controlled trial, PVE – portal vein embolisation, RCT – randomised controlled trial, RoB – risk of bias, TLV – total liver volume.

Notes: For both efficacy and safety outcomes, study inclusion was amended to also include retrospective non-randomised comparative studies due to an absence of prospective studies. However, retrospective studies in which critical concerns about risk of bias were identified (non-comparable patient groups with respect to critical clinical characteristics or low statistical power [n≤12]) were excluded.

3 Methods

3.1 Research questions

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [58].

Please refer to the Appendix for the Research questions (Table A-9 to Table A-12).

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted between the 8th and 9th of December 2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

Einschlusskriterien

The systematic search was, in Medline and Embase, limited to systematic reviews and meta-analyses, randomised controlled trials and prospective non-randomised studies published in English. No date limit was applied. After removing duplicates, a total of 799 citations were included. The specific search strategy employed can be found in the Appendix.

Handsuche

Additional pearling of the reference lists of included studies was undertaken to identify any retrospective studies; resulting in an additional nine studies being identified (total of 808 citations).

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO ICTRP; EU Clinical Trials) was conducted on the 25th of January 2022, resulting in two potential studies.

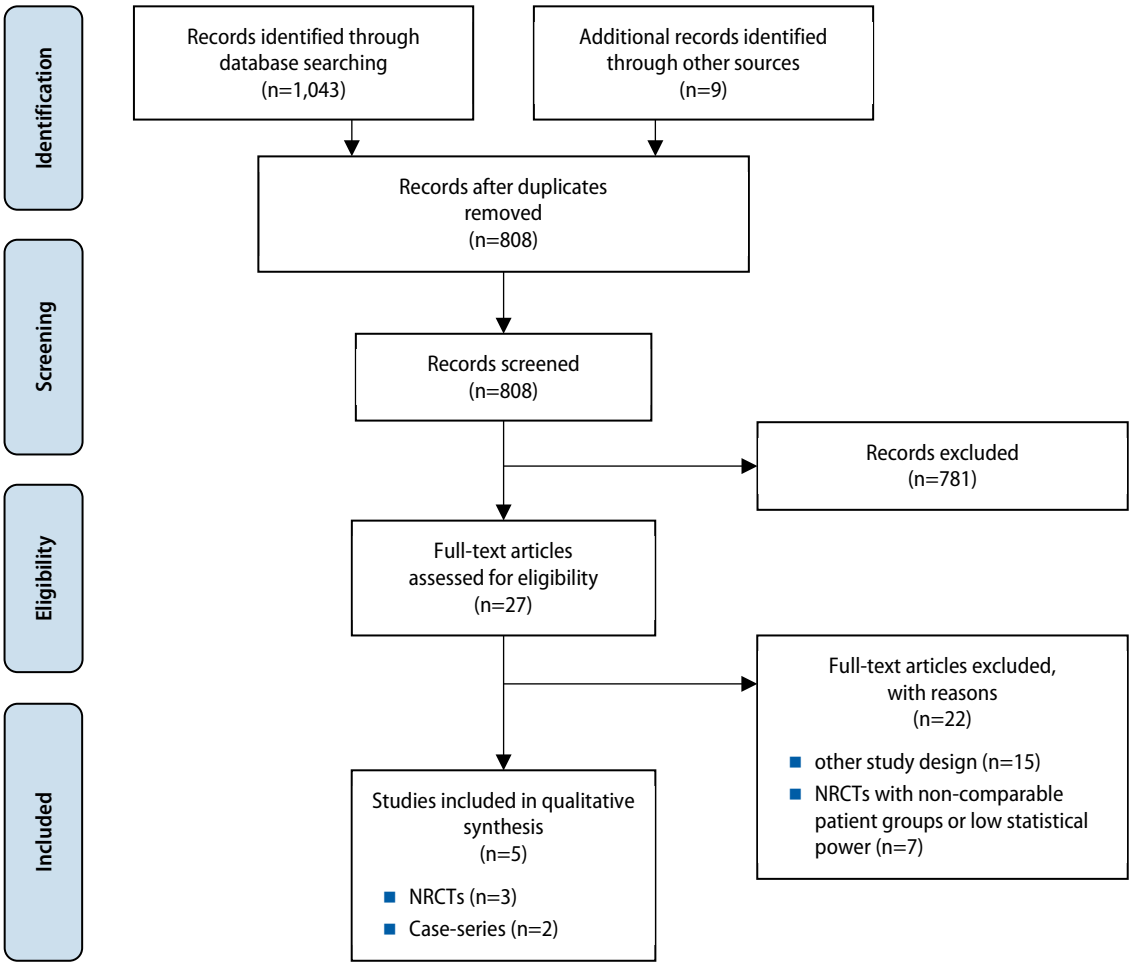
3.2.2 Flow chart of study selection

Literaturauswahl: 5 Studien eingeschlossen

Overall, 808 citations were identified. The references were screened by two independent researchers (ER, JD), and in case of disagreement, a third researcher was involved to resolve the differences. Out of 808 hits, a total of 27 full-text studies were reviewed, and eventually five were considered for the qualitative evidence synthesis.

Seven retrospective NRCTs were excluded after full-text review due to critical concerns about risk of bias.

The selection process is displayed in Figure 3-1.



Abbreviation: NRCTs – non-randomised controlled trials

Notes: NRCTs in which critical concerns about risk of bias were identified (non-comparable patient groups with respect to critical clinical characteristics or low statistical power [n≤12]) were excluded at full-text review.

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

3.2.3 Analysis

Datenextraktion und -kontrolle

Data from the included studies were extracted into a priori designed data extraction tables (see Table A-1 and Table A-2 in the Appendix). One researcher extracted the data (ER), and another researcher verified the data (DS).

Darstellung der Ergebnisse

The reporting of results was limited to a narrative review given the low level and quantity of evidence; no pooling of results or statistical comparisons were made.

Bewertung von Studienqualität und Verzerrungsrisiko

The quality of the included studies was systematically assessed with the ROBINS-I tool (see Table A-3 and Table A-4 in the Appendix). The internal validity and risk of bias of the included studies were assessed by two independent researchers (ER, MV). In case of disagreement, a third researcher was involved in resolving the differences.

Furthermore, the quality of the NRCTs excluded at full-text review was also assessed with the ROBINS-I tool (Table A-5 in the Appendix) to check that no high-quality studies had inadvertently been excluded.

3.2.4 Synthesis

Evidenzsynthese mittels GRADE

The questions were answered in plain text format with reference to GRADE evidence tables included in the Appendix (Table A-6). Results are summarised in Quality of evidence.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Effectiveness outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidungsrelevante Wirksamkeits-Endpunkte

- Life expectancy/overall survival
- PHLF
- Rapid tumour growth due to PVE
- Ineligibility for planned resection due to:
  - Disease progression after embolisation (potentially due to PVE)
  - Insufficient hypertrophy of the FLR

Life expectancy/overall survival is included as a crucial outcome in the PICO criteria. However, no data on oncological outcomes such as overall survival were available in the included studies. Survival data were limited to postoperative mortality, which is included as a *crucial* safety outcome.

Gesamtüberleben

PHLF is one of the most serious life-threatening complications after major hepatectomy. It occurs as a result of an insufficiently functioning remnant liver after liver resection, and can manifest as prolonged prothrombin time, elevated serum lactate, decreased serum albumin, low blood sugars and/or hepatic encephalopathy [19]. Studies reporting this outcome defined PHLF according to either the "50-50" criteria (prothrombin time value <50% and serum bilirubin concentration >50 µmol/L on postoperative day five) or the International Study Group on Liver Surgery's (ISGLS) definition (international normalised ratio with hyperbilirubinemia at least five days after surgery)[19, 45, 47].

PHLF: schwerste lebensbedrohliche Komplikation

Rapid tumour growth due to PVE: PVE induces hypertrophy of the FLR by obstructing portal blood flow to the tumour-bearing part of the liver. This obstruction stimulates haemodynamic changes, which result in an increased blood supply to metastases – this may not only induce disease progression in the embolised lobe, but also stimulate disease progression in the FLR and increase the risk of recurrence.

Tumorwachstum aufgrund von PVE

None of the included studies reported data on tumour growth due to PVE.

Ineligibility for planned resection was added as as a *crucial* outcome in the absence of data on tumour growth due to PVE. A previous systematic review on HPVE included dropout rate from surgery and its causes as a primary outcome measure [40]. This outcome provides information on the number of patients who do not undergo hepatectomy despite preoperative embolisation; this would be due, primarily, to either disease progression after HPVE or PVE or insufficient hypertrophy of the FLR. Included studies reported absolute numbers of patients who did not progress to hepatectomy, including reasons why resection could not be performed.

Major-Hepatektomie nicht immer möglich

wichtige Endpunkte

In addition to the crucial outcomes, the following outcomes were also considered important to answer the research questions:

- **Percentage of hypertrophy** defines the degree to which the FLR-V increases after an embolisation procedure. It is the ratio of the post-procedure FLR-V to the initial FLR-V
- **Residual liver volume** corresponds to the absolute FLR-V before and after embolisation. It is the main predictor of hepatic dysfunction [19, 59]
- **FLR/TLV ratio** defines the FLR-V as a percentage of the TLV. This ratio is often used in defining the indications for PVE (e.g. <20-25% in a healthy liver)
- **Change in FLR-F** was added as an important outcome. It indicates the change in the function of the FLR after HPVE or PVE in comparison to baseline levels
- **R0 resection rate** indicates a microscopically margin-negative resection, in which no gross or microscopic tumour remains in the primary tumour bed; in other words, a resection for cure or a complete remission[60, 61]. In the one study reporting this outcome, R0 resection was defined as a margin >1 mm [45]
- **Tumour progression** disease progression after PVE or HPVE precluding hepatectomy is reported under the added *crucial* outcome ineligibility for planned resection
- **Length of hospital stay after embolisation** calculated from the first postoperative day until the day of discharge or death [45].

Liver volume and function analyses were, in the three comparative studies, ascertained by computed-tomography (CT) scan (volume) [45, 49] or 99mTc-mebrofenin single-photon emission computed tomography/computed tomography (SPECT-CT) system (volume and function) [47].

4.1.2 Safety outcomes

entscheidungsrelevante Sicherheits-Endpunkte

The following outcomes were defined as *crucial* to derive a recommendation:

- 30- or 90-day mortality
- Morbidity (after embolisation or hepatectomy)
- Surgical or device-related AEs

Mortalität

Mortality is a highly important patient-relevant outcome measure when assessing the safety of the whole surgical procedure (embolisation followed by resection).

Morbidität

Morbidity: complications or undesirable side effects following surgery or medical treatment. For *crucial* morbidity outcomes, both serious AEs and any specific hepatobiliary complications described by the included studies were considered.

unerwünschte schwere Ereignisse

Serious AEs are defined according to the Clavien-Dindo classification and correspond to any complication ≥III. These include events that require surgical, endoscopic or radiological intervention, are life-threatening, or result in the death of a patient [62]. All included studies graded post-hepatectomy complications using the Clavien-Dindo classification of surgical complications. In addition, one study used this system to grade the severity of AEs after embolisation [45].

hepatobiliäre Komplikationen variierten

The reporting of hepatobiliary complications varied across studies – one comparative study reported a composite 'hepatobilary complications' outcome [49]; a second reported on intra-abdominal collection, biliary leak, ascites, and liver failure [45]; the third reported only liver failure [47].

operations- oder gerätebedingte unerwünschte Ereignisse

Surgical- or device-related AEs include the following: haemobilia and biliary leak, biloma, infection, pneumothorax and/or haemothorax, vascular and arterial injuries, haemorrhage, cholangitis, liver abscess, hepatic infarction, non-target embolisation, portal or mesenteric venous thrombosis, recanalisation, as well as portal hypertension.

wichtige Endpunkte

In addition to the crucial outcomes, the following outcomes were also considered important to answer the research questions:

- Withdrawal due to treatment-related AEs
- Recovery time before being able to do the resection

4.2 Included studies

4.2.1 Included effectiveness studies

Study characteristics and results of included studies are displayed in Table A-1, quality in Table A-3, and in the evidence profile in Table A-6.

Effektivität: 3 retrospektive nicht-randomisierte kontrollierte Studien

Three non-randomised, comparative, single-centre retrospective studies, including 51-73 patients, were included for effectiveness [45, 47, 49]. They all used PVE as a comparator to simultaneous HPVE. Indications for hypertrophy before major hepatectomy were as follows:

Indikationen

- Small FLR <25% of a normal liver or <35-40% of a diseased liver, and/or an FLR-V compared to bodyweight <0.5% in two studies [45, 49],
- Small FLR <30% of TLV or FLR-F <2.69%/min/m^2 (99mTc-mebrofenin clearance rate). A 20% functional margin for planned resection at risk was considered (FLR-F <3.23%/min/m^2) in one study [47].

Gruppenunterschiede vor Embolisation

In one study [45], patients underwent HPVE if their FLR was <25%, while patients with an FLR between 25-35% had PVE. This resulted in significant differences between groups at baseline for FLR-V, FLR/TLV ratio, and FLR/bodyweight ratio measures. Except for the matching process, where demographic and disease characteristics were comparable between the two groups, no specific statistical analyses were performed to reduce the bias.

Patient*innen-Charakteristika meist vergleichbar

In a second study [47], patient characteristics were comparable between groups, except for baseline FLR-F, which was lower in the HPVE group (1.9%/min/m^2 vs 2.59%/min/m^2, p<0.001). Authors stated that this was because they tended to propose the more aggressive HPVE technique to patients with a lower FLR-F. Authors adjusted their analysis for baseline FLR-F to limit the selection bias.

Ausschlusskriterien

Two studies excluded patients with cirrhosis [45, 47]. One of these also excluded patients with liver fibrosis [45]; the other also excluded patients with Klatskin tumours and those undergoing two-stage hepatectomy [47]. In the third study, 9.7% of patients had cirrhosis [49]. Additionally, 27.7% of patients had non-alcoholic steatohepatitis (NASH) [49]. Patients with chemoembolisation plus embolisation were excluded [49].

Patient*innen-Charakteristika

Patients undergoing PVE had a median age varying between 61-66 years old, were mainly men (68-72.7% across the studies) and had a median body mass index (BMI) ranging from 24 to 25.5kg/m^2 [45, 47, 49]. Patients undergoing HPVE had a median age varying between 62-66 years old, were mainly men (52.0-72.4% across the studies) and had a median BMI ranging from 24.0-26.3kg/m^2 [45, 47, 49]. In all three studies, there were no significant differences between PVE and HPVE groups in terms of age, gender or BMI.

Lebermetastasen als Haupttumorart

Liver metastases were the main tumour type found in enrolled patients in the three studies [45, 47, 49], followed by intrahepatic cholangiocarcinoma (ICC) and HCC. However, data for the PVE group were missing from one publication [49].

3 Monate Follow-up nach Resektion

Follow-up time after resection was three months for the three studies [45, 47, 49]. None of the studies reported any patient loss, but in one study, 23.3% of the morphological-functional evaluations.were missing for 12/51 (23.5%), 15/51 (29.4%) and 13/51 (25.5%) patients at days seven, 14, and 21, respectively [47]. Several reasons for this were mentioned, including patient's opposition, 99mTc-mebrofenin shortage, or earlier achievement of the safe FLR-F threshold. Missing values were handled using multiple imputation analysis [47]. Furthermore, not all patients were able to undergo the planned resection (due to either disease progression or insufficient hypertrophy), meaning that not all patients are included with respect to the post-surgical outcomes.

Resektion nicht bei allen Patient*innen möglich

4.2.2 Additional included safety studies

Study characteristics and results of included studies are displayed in Table A-2, quality in Table A-4, and in the evidence profile in Table A-6.

Sicherheit: zusätzlich 2 prospektive Fallserien

Two prospective observational studies (case series) were additionally included in the report [63, 64]. In one case series, HPVE was performed sequentially, with a mean of 13.5±4.2 days between PVE and HVE [64]; in the second case series, a simultaneous procedure was performed [63]. Both studies aimed for a right hepatectomy or more extensive liver surgery.

Einschlusskriterien

Inclusion criteria in the case series considering simultaneous HPVE were an FLR <35-40% of [63]. In the case series considering sequential HPVE, PVE was performed if the FLR was <40% of TLV, and the HVE was performed sequentially one to two weeks after PVE performed if FLR was still <40% of TLV (<45% if serious comorbidities or planning for hepaopancreatoduodenectomy) [63]. Both studies aimed for a right hepatectomy or more extensive liver surgery.

Patient*innen-Charakteristika

Both studies enrolled twelve patients (83.3% of patients in each study were men), with mean ages of 55.5 and 60.5 years old [63, 64]. Patients with colorectal liver metastasis and no background liver disease were enrolled in one case series [63], while in the second, patients had mainly perihilar cholangiocarcinoma (66.7%); 16.7% of patients had cirrhosis [64].

Behandlungen vor Embolisation

One case series reported that before the embolisation procedure, all patients had chemotherapy, 50% had liver surgery or radiotherapy, and 50% had a hepatic arterial infusion pump [63]. None of these characteristics was reported in the second case series [64].

Follow-up

Patients length of follow-up ranged from 28 days to 20 months. In one of the case series, a single patient was lost to follow-up [64].

Two and three patients were ineligible for planned resection across the two case series due to disease progression or insufficient hypertrophy after HPVE [63, 64]. Post-surgical safety outcomes are therefore only available for ten and nine patients across the two studies, respectively. In one case series, one patient with insufficient FLR underwent resection 17 months after HVE (with TACE in the interim) [64].

keine Resektion in 5 Patient*innen möglich

4.3 Results

Mortality

Post-surgical mortality (30- to 90-day mortality) is reported as a patient safety outcome.

Mortalität

Morbidity

The *crucial* outcomes of PHLF and ineligibility for planned resection after embolisation (due to either disease progression or insufficient hypertrophy) were considered when assessing morbidity outcomes.[21] The *important* outcome of RO resection rate was also considered. Additionally, laboratory results from post-embolisation day one and postoperative day five are considered. No data on how HPVE affects disease recurrence was retrieved.

PHLF, Inoperabilität nach Embolisation und R0-Resektionsrate

Post-hepatectomy liver failure

Two of three comparative studies reported PHLF [45, 47]. The third comparative study reported hepatobiliary complications as a composite outcome, precluding PHLF data extraction [49]. PHLF results are summarised in Table 4-1.

verschiedene Definitionen von PHLF (2 Studien)

Table 4-1: Post-hepatectomy liver failure outcomes

Study ID	Patient number	PHLF rate n, %	Comments
Guiu et al. [47]	HPVE: 27 PVE: 20	HPVE: 0, 0% PVE:0, 0%	None
Laurent et al. [45]	HPVE: 32 PVE: 32	HPVE: 0, 0% PVE: 7, 21.9% p=0.012	Grade A (HPVE: 0; PVE: 3; p=NS) Grade B (HPVE: 0; PVE: 3; p=NS) Grade C (HPVE: 0 vs PVE 1; p=NS)
Le Roy et al. [49]	NA	NE	PHLF reported within a composite outcome measure

Abbreviations: HPVE – hepatic and portal vein embolisation, NA – not applicable, NE – not estimable, PHLF – posthepatectomy liver failure, PVE – portal vein embolisation,

Notes: Patient numbers reflect the number of patients undergoing planned resection in each study. Graded as proposed by the International Study Group of Liver Surgery.

[21] **D0005** – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

statistisch signifikanter (s.s.) Unterschied (1 Studie)

One study found a statistically significant difference between HPVE and PVE (HPVE 0/32 [0%] vs PVE 7/32 [21.9%], p=0.012) [45]. Among the seven patients with PHLF in the PVE group, six had grade A or B liver insufficiency, and one had grade C (based on the grading system proposed by the International Study Group of Liver Surgery). The second study did not record any PHLF in either group (HPVE 0/27[0%] vs PVE 0/20 [0%]) [47].

Hepatic resection ineligibility after embolisation

unmögliche Leberresektion aufgrund unzureichender FLR-Hypertrophie/Funktion oder Krankheitsfortschritt (3 Studien)

In all three comparative studies, some patients did not progress to hepatectomy due to either insufficient FLR hypertrophy [45, 49] or function [47], or disease progression – peritoneal carcinomatosis or intrahepatic progression – discovered either before or at the time of surgery. Reasons for ineligibility for resection after embolisation are summarised in Table 4-2.

Table 4-2: Reasons for ineligibility for planned resection after embolisation

Outcomes	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
Patient number	HPVE: 29; PVE: 22	HPVE: 37; PVE: 36	HPVE: 31; PVE: 41
Insufficient FLR			
Insufficent FLR hypertrophy:	NA	HPVE: 0, 0%; PVE: 1, 2.8%	HPVE: 0, 0%; PVE: 2, 4.9%
Insufficent FLR-F:	HPVE: 1, 3.4%; PVE: 2, 9.1%	NA	NA
Disease progression			
Peritoneal carcinomatosis	HPVE: 1, 3.4%; PVE: 0, 0%	HPVE 0, 0%; PVE 1, 2.8%	HPVE: 3, 9.7%; PVE: 0, 0%
Intrahepatic progression	HPVE: 0, 0%; PVE: 0, 0%	HPVE: 5, 13.5%; PVE: 2, 5.6%	HPVE: 3, 9.7%; PVE: 4, 9.8%
Other			
Contraindication at surgery (reason NR)	NA	NA	HPVE: 0, 0%; PVE: 4, 9.8%

Abbreviations: HPVE – hepatic and portal vein embolisation, PVE – portal vein embolisation, NA – not applicable, NR – not reported

kein Gruppenunterschied (1 Studie)

Only one study compared these outcomes between groups [49]. Neither the number of patients having disease progression nor the number with insufficient hypertrophy differed significantly between groups.

R0 resection rate

vollständige Remission (1 Studie)

Patient complete remission was reported by one comparative study (PVE 30/32 [93.8%] vs HPVE 31/32 [96.9%]) [45].

Additional morbidity outcomes

Markers of liver function after embolisation

kein s.s. Gruppenunterschied (2 Studien)

Laboratory data – transaminase (alanine and aspartate), prothrombin, bilirubin and gamma-glutamyl transferase levels – measured one day after embolisation were reported by two comparative studies [45, 49]. None of the markers was found to differ statistically significantly between groups in either study.

Markers of liver function after hepatectomy

nur prozentuale Prothrombin-Wert s.s. (1 Studie)

One study reported aspartate aminotransferase, alanine aminotransferase, prothrombin, bilirubin and gamma-glutamyl transferase levels measured on postoperative day five [45]; another reported only bilirubin and prothrombin levels (again, measured on postoperative day five) [47]. Prothrombin percentage

was the only laboratory measure to differ significantly between groups (HPVE 89% [range: 52-100%] vs PVE 81% [27-100%], p=0.028) in one study [45]. The difference in prothrombin levels was not statistically significant in the second study [47]. The difference in prothrombin levels was not statistically significant in the second study [47].

Function

FLR-Hypertrophie, verbleibendes Lebervolumen, FLR-Verhältnis und -Funktion

Outcomes of the volume and functional analyses were considered when assessing the effect of HPVE on patients' body functions.[22] These included the *important* outcomes of the degree of hypertrophy of the FLR, residual liver volume, FLR/TLV ratio, and change in FLR-F. Total liver function and kinetic growth rate were also assessed. No data was retrieved to answer the questions pertaining to activities of daily living.[23]

Percentage hypertrophy of the FLR

The degree of hypertrophy of the FLR was reported by all three comparative studies [45, 47, 49].

Zuwachs an FLR-Volumen: s.s. Unterschied nach 14 und 21 Tagen (1 Studie)

One study reported FLR growth at days seven, 14 and 21 after embolisation, finding statistically significant differences between groups at days 14 (HPVE 50% [range: –4.4 to 90.6%] vs PVE 14.2% [–23.5 to 58.6%], p=0.002), and 21 (HPVE 52.6% [1.0 to 175.6%] vs PVE 18.6% [–10.7 to 102.2%], p=0.001) post-embolisation [47]. No statistical difference was shown between day seven and baseline.

Grad der FLR-Hypertrophie: s.s. Unterschied (2 Studien)

The remaining two studies measured the degree of hypertrophy at a mean of 30.6 (HPVE) vs 30.5 (PVE) days (p=0.950) and 26 (HPVE) vs 27 (PVE) days (p=0.760) after embolisation. A statistically significant difference in the degree of hypertrophy of the FLR between HPVE and PVE groups was found by both studies [45, 49]. Degrees of hypertrophy of 61.2% (median) and 51.2% (mean) for HPVE compared to 29.0% (median) and 31.9% (mean) for PVE (p<0.0001 and p=0.018, respectively) were described by these two studies [45, 49]. The degree of hypertrophy of segment IV only was analysed by one study but no statistical difference between the two groups was found[49].

Residual liver volume

absolutes FLR-Volumen: kein s.s. Unterschied (2 Studien)

Absolute FLR-V before and after embolisation were reported by two studies [45, 49]. In one study there was a significant difference at baseline which disappeared after embolisation (baseline [HPVE vs PVE]: 387 vs 468mL, p=-0.008; post-embolisation: 611 vs 636.5mL, p=0.867)[45]. No difference between groups at either time point was reported by the second study [49].

FLR/TLV ratio

s.s. Unterschied (1 Studie)

The change in the FLR/TLV ratio after HPVE and PVE procedures (compared to baseline) was reported by one study. A statistically significant difference between groups was observed (HPVE: 10.0 ± 6% vs PVE: 7.5±5%; p=0.047) [49].

A second study reported absolute FLR/TLV ratios pre- and post-embolisation [45]. A statistically significant difference in the FLR/TLV ratio at baseline

[22] **D0011** – What is the effect of the technology on patients' body functions?

[23] **D0016** – How does the use of technology affect activities of daily living?

(HPVE 22.9% vs PVE 31.0%, p=0.0001) was observed which disappeared after embolisation (HPVE 39.9% vs PVE 39.5%, p=0.460) [45].

The final study reported only the baseline FLR/TLV ratio [47].

FLR function

s.s. Unterschied (1 Studie)

Change in FLR-F after embolisation was reported in one study [47]. A statistically significant difference in the change in FLR-F in favour of HPVE was found on days seven, 14 and 21 after the embolisation (p=0.02, p=0.006, and p<0.001, respectively). At baseline, FLR-F was statistically significantly greater in the PVE group (HPVE 1.9 [1.3-2.5] vs PVE 2.6 [1.3-3.1], p<0.001).

Additional volumetric and functional results

s.s. Unterschied nach 21 Tagen (1 Studie)

Change in TLV after embolisation was reported in one study [47]. A statistically significant difference in the change in TLV between HPVE and PVE was found at day 21 post-embolisation (p=0.03). Differences between groups at days seven and 14 post-embolisation were not significant.

kein s.s. Unterschied (1 Studie)

Change in total liver function after embolisation was reported in one study [47]. No statistically significant differences were found at any time point.

s.s. Unterschied (1 Studie)

Kinetic growth rate (mean degree of hypertrophy divided by the number of weeks) was reported in one study [49]. The difference in kinetic growth rate after HPVE vs after PVE was found to be statistically significant (mean 19% per week vs 8% per week; p=0.026).

Health-related quality of life

keine Evidenz

No data was retrieved regarding patients' health-related or disease-specific quality of life.[24]

Patient satisfaction

keine Evidenz

Regarding patient satisfaction, no evidence was found.[25]

Patient safety

Mortalität, operations-/ gerätebedingte, postoperative und unerwünschte Ereignisse, Genesungszeit und Behandlungsabbruch

Concerning patient safety, the *crucial* outcomes of 30- or 90-day mortality (post-hepatectomy), and serious, surgical- or device-related AEs (post-embolisation and post-hepatectomy) were considered.[26] The *important* outcomes of minor complications (post-embolisation), withdrawal due to treatment-related AEs, and recovery time before being able to do the resection were also considered. Additionally, pain and minor complications (post-hepatectomy) are also reported. No data regarding susceptible patient groups more likely to be harmed by the technology were identified.[27]

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[24] **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

[25] **D0017** – Was the use of the technology worthwhile?

[26] **C0008** – How safe is the technology in comparison to the comparator(s)?
D0001 – What is the expected beneficial effect of the technology on mortality?

[27] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

Postoperative mortality

Mortalität in allen 5 Studien berichtet

The *crucial* outcome mortality (follow-up: range 30 to 90 days) was reported in all five studies included for the assessment of safety [45, 47, 49, 63, 64]. Results from each of the included studies are summarised in Table 4-3.

Table 4-3: Postoperative mortality outcomes

Study ID	Patient number	Postoperative deaths (n, %)	Follow-up period
Retrospective comparative studies			
Guiu et al. [47]	HPVE: 27 PVE: 20	HPVE: 0, 0% PVE: 1, 5.0%	90 days
Laurent et al. [45]	HPVE: 32 PVE: 32	HPVE: 0, 0% PVE: 1, 3.1%	90 days
Le Roy et al. [49]	HPVE: 25 PVE: 31	HPVE: 3, 12.2% PVE: 2, 6.5%	90 days
Case series			
Ghosn et al. [63]	HPVE: 10	HPVE: 1, 10.0%	NR
Hwang et al. [64]	HPVE: 9	HPVE:1, 11.1%	28 days–20 months

Abbreviations: HPVE – hepatic and portal vein embolisation, PVE – portal vein embolisation, NR – not reported

Notes: Patient numbers reflect the number of patients undergoing planned resection in each study. The one death reported in Ghosn et al. occurred 1 month postoperatively. The one death reported in Hwang et al. occurred 28 days postoperatively.

7 Todesfälle (3 Studien), jedoch kein s.s. Unterschied (2 Studien)

Ninety-day mortality was reported by all three comparative studies, ranging from HPVE 0-12.2% in patients who had undergone preoperative HPVE and between 3.1-6.5% in those who had undergone PVE [45, 47, 49]. In two of the three comparative studies, differences in 90-day mortality between HPVE and PVE groups were not statistically significant (HPVE 0/32 vs PVE 1/32, p=1; HPVE 3/25 vs PVE 2/31, p=0.228) [45, 49]. In the third comparative study, statistical significance was not reported (HPVE 0/27 vs PVE 1/20, p=NR) [47]. The cause of death in the PVE group was specified in two studies – pulmonary embolism, and grade C PHLF even though patients had a theoretical sufficient hypertrophy authorising resection [45, 47]. Causes of death in the remaining two patients who underwent PVE and in the three patients who underwent HPVE were not reported [49].

2 Todesfälle

The follow-up period after resection was not specified in the two case series, although the deaths occurred at 28 days and one month after hepatectomy (within 30 days of the surgery) [63, 64]. The two studies highlighted that neither death was procedure-related.

keine Evidenz

Insufficient data were available to assess the effect of HPVE on mortality due to causes other than the target diseases.[28]

[28] **D0003** – What is the effect of HPVE on the mortality due to causes other than the target disease?

Major adverse events after embolisation

keine schweren unerwünschten Ereignisse (4 Studien), jedoch in 1 Studie

No major AEs were reported in four out of five studies [47, 49, 63, 64]. Two Clavien-Dindo grade ≥III events (i.e. serious AEs) after embolisation were reported by one study, both of which occurred in the PVE group. The difference between groups was not significant (HPVE 0/37 [0%] vs PVE 2/36 [5.6%], p=0.493) [45].

Surgical- or device-related adverse events after embolisation

in 5 Studien berichtet

All five studies reported surgical- or device-related AEs after embolisation [45, 47, 49, 63, 64]. Table 4-4 summarises all the surgical- or device-related AEs reported.

Table 4-4: Surgical- or device-related adverse events after embolisation

Study ID	Patient number	Surgical- or device-related AE rate (n, %)	Description of events
Retrospective comparative studies			
Guiu et al. [47]	HPVE: 29 PVE: 22	HPVE: 6, 20.7% PVE: 3, 13.6%	Minor peri-hepatic hematoma: HPVE: 2; PVE: 1 Transient grade 1-2 asthenia: HPVE : 4; PVE: 2
Laurent et al. [45]	HPVE: 37 PVE: 36	HPVE: 2, 5.4% PVE: 2, 5.6%	Erratic embolisation in the segmental branch: HPVE: 1; PVE: 2 Erratic embolisation in the segmental branch: HPVE: 1
Le Roy et al. [49]	HPVE: 31 PVE: 41	HPVE: 3, 9.7% PVE: 1, 2.4%	High intraoperative portal pressure: HPVE:2; PVE: 1 Unintentional embolisation of the middle hepatic vein instead of RHV: HPVE: 1
Case series			
Ghosn et al. [63]	HPVE: 12	HPVE: 2, 16.6%	Non-target embolisation in segment 2: 1 Bland thrombosis of the proximal right portal vein: 1
Hwang et al. [64]	HPVE: 12	HPVE: 1, 8.3%	MHV was erroneously embolized instead of the RHV: 1

Abbreviations: AE – adverse event, HPVE – hepatic and portal vein embolisation, MHV – middle hepatic vein, PVE – portal vein embolisation, RHV – right hepatic vein

nicht-zielgerichtete/ fehlerhafte Embolisation oder hoher Blutdruck

Non-target embolisation was the main AE reported in comparative studies, ranging from 3.2-5.4% in HPVE group vs 0-5.6% in PVE group [45, 49]. An erroneous embolisation – non-target embolisation in one study; error in embolisation location in the other – was reported for 8.3% of patients in each case series [63, 64]. High intraoperative portal pressure was reported in one study and occurred in two (6.5%) vs one (2.4%) patients in HPVE and PVE groups, respectively [49].

Postoperative adverse events

in 5 Studien berichtet Clavien-Dindo Klassifikation

All five studies graded post-hepatectomy complications using the Clavien-Dindo classification of surgical complications [45, 47, 49, 63, 64]. Serious AE rates are presented in Table 4-5.

Table 4-5: Serious adverse events after surgery

Study ID	Patient number	Major postoperative AE rate (n, %)	Description of events
Retrospective comparative studies			
Guiu et al. [47]	HPVE: 27 PVE: 20	HPVE: 3, 3.7% PVE: 3, 15.0%	NR
Laurent et al. [45]	HPVE: 32 PVE: 32	HPVE: 6, 19.0% PVE: 10, 31.0%	HPVE: NR PVE: limited description provided, includes: Liver failure & portal thrombosis (n=1) Liver failure & death (n=1)
Le Roy et al. [49]	HPVE: 25 PVE: 31	HPVE: 5, 20.0% PVE: 3, 9.7%	NR
Case series			
Ghosn et al. [63]	HPVE: 10	HPVE: 7, 70.0%	Postoperative abscess (n=1) Leukocytosis requiring percutaneous drainage (n=4) Liver failure & acute kidney insufficiency (n=1) Death (n=1)
Hwang et al. [64]	HPVE: 9	HPVE: 1, 11.1%	Death (n=1)

Abbreviations: HPVE – hepatic and portal vein embolisation, PVE – portal vein embolisation, NR – not reported

hepatobiliär-bedingte unerwünschte Ereignisse (2 Studien):

In addition to serious AEs reported according to Clavien-Dindo classifications, specific hepatobiliary-related AEs were reported in two of three comparative studies [45, 49].

z. B. PHLF: s.s.

One comparative study reported the following AEs after surgery [45]:

- biliary leak (HPVE 1/32 [3.1%] vs PVE 3/32 [9.4%], p=0.614)
- ascites (HPVE 2/32 [6.3%] vs PVE 2/32 [6.3%], p=1)
- intra-abdominal collection (HPVE 3/32 [9.4%] vs PVE 2/32 [6.3%], p=1)
- portal thrombosis treated by surgical thrombectomy (Clavien-Dindo Grade IV; occuring in one patient with PHLF after PVE)
- PHLF (HPVE 0/32 [0%] vs PVE 7/32 [21.9%], p=0.012)

Two of the seven patients with PHLF were classified as Clavien-Dindo grade ≥III (including one patient who also had portal thrombosis). The other hepatobiliary-related AEs (biliary leak, ascites, intra-abdominal collection) may have also been of a serious severity (grade ≥III), however, this level of detail was not provided [45].

z.B. hepatobiliäre Komplikationen: nicht s.s.

A second comparative study reported hepatobiliary complications (comprising ascites, encephalopathy, jaundice, or liver failure defined using the "50-50" criteria, a peak bilirubin value of ≥120mmol/l on postoperative day seven, and/or by grade C liver failure as defined by the International Study Group of Liver Surgery) as a composite outcome, finding no statistically significant difference between groups (HPVE 9/25 vs PVE 9/31, p=0.436) [49].

kein PHLF (1 Studie)

In the third comparative study, no patient experienced PHLF after either HPVE or PVE [47].

Recovery time before resection

HPVE: durchschnittlich 36 Tage (2 Studien) …

The time between embolisation and resection was reported by two of three comparative studies [45, 47]. Following HPVE, patients waited a median of 32 days or a mean of 36 days, whilst after PVE, they waited a median of 36 days or a mean of 45 days. Neither study reported a statistically significant difference between groups. The third comparative study did not report this outcome [49].

… 39 und 22 Tage (2 Studien)

The two case series reported mean waiting times of 39.0 and 22.1 days [63, 64]. In the study with the shorter wait period, HPVE had been performed sequentially to PVE, with a mean of 13.5 days between the two embolisation procedures [64].

Withdrawal due to treatment-related adverse events

1 Patient*in (1 Studie)

In one observational study, one patient could not progress to hepatic resection following an error in embolisation location, which was coupled with rapid tumour progression [64].

Additional safety outcomes

Pain

kein s.s. Unterschied (1 Studie)

One comparative study measured patients' pain after embolisation using a ten-point visual analogue scale (VAS) [45]. No statistically significant differences in the number of patients having pain of either low (VAS score of 1-3), moderate (VAS score of 4-6) or high (VAS score of 7-10) intensity were reported.

Minor adverse events after embolisation

7 Patient*innen (2 Studien)

Both case series reported that some patients experienced minor AEs after the HPVE procedure. In one study, two of twelve patients (16.6%) had right upper quadrant pain requiring morphine [63]. In the other study, five of twelve patients (41.6%) had transient symptoms and signs, including mild abdominal pain, low-grade fever and/or nausea [64].

fast alle Patient*innen Clavien-Dindo Grad I oder II (1 Studie)

One comparative study classified patients using the Clavien-Dindo classification system after embolisation. Almost all patients were classified as grade I or II (HPVE 37/37 [100%] vs PVE 34/36 [94.4%]).

Blood loss during hepatectomy

kein s.s. Unterschied (2 Studien)

Blood loss in millilitres lost was reported by two comparative studies, without any statistical difference between HPVE and PVE groups [45, 49].

Bluttransfusion: 5 Patient*innen (2 Studien)

The number of patients requiring transfusion was reported by both case series (one of ten [10.0%] and four of nine [44.4%]) [63, 64].

Additional outcomes

Technical success rate for embolisation

100 % technische Erfolgsquote (2 Studien)

Two of three comparative studies reported this outcome. Both studies reported technical success rates of 100% for both HPVE and PVE procedures [45, 47]. Only one of these studies provided a definition for technical success – complete embolisation of the portal and hepatic vessels [47]. Only one of these studies provided a definition for technical success – complete embolisation of the portal and hepatic vessels [47].

Hospital stay after embolisation

This outcome was reported by the three comparative studies, but only one study specified there was no statistical difference between HPVE and PVE [45]. In two of the studies [45, 47], patients stayed between one to ten days (with a median length of stay varying between 1.4-2.0 days), whilst in the third study, all patients were discharged the following day [49].

kein s.s. Unterschied (1 Studie)
durchschnittlich 1-2 Tage (2 Studien)

Investments and tools required

The types of data/records or registry needed to monitor the use of HPVE and PVE was not assessed for this report.[29]

nicht bewertet

[29] **B0010** – What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

5 Quality of evidence

niedriges bis moderates Verzerrungsrisiko

Risk of bias (RoB) for individual studies was assessed with the ROBINS-I tool. Results are presented in Table A-3 and Table A-4. All three comparative studies were ranked as moderate RoB [45, 47, 49], while the two observational studies were ranked as low RoB [63, 64]. Bias due to confounding and bias due to patient selection were the two main reasons for downgrading the comparative studies. Additionally, one study was downgraded for bias due to missing data [47]. Bias due to confounding and bias due to patient selection were the two main reasons for downgrading the comparative studies. Additionally, one study was downgraded for bias due to missing data [47].

The two observational studies were both single-centre studies, and the outcome assessors were not blinded to the intervention that patients received [63, 64]. However, this did not affect the ranking as they were only assessed for safety outcomes.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [65] for each endpoint individually. Each outcome was rated by a single researcher (ER), and reviewed by a second researcher (DS). Any areas of uncertainty were discussed. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [65].

GRADE: 4 Kategorien

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 in the evidence profile in Appendix Table A-6.

(sehr) niedrige Qualität der Evidenz

Here, only the outcomes defined as *crucial* to derive a recommendation were considered when rating the overall strength of evidence. The study design of the included studies (retrospective non-randomised comparative trials or case series) impacted the strength of evidence, with the grading of all outcomes starting as low. The overall strength of evidence for the effectiveness and safety of HPVE in comparison to PVE ranged from very low to low.

Table 5-1: Summary of findings table: HPVE versus PVE

Outcome	Patient Number (Study)	Absolute effect (HPVE), range	Absolute effect (PVE), range	Certainty	Comments
Efficacy					
PHLF	HPVE: 59 PVE: 52 (k=2)	0%	0% to 21.9%	⨁◯◯◯ Very low	RoB: Lack of allocation concealment and blinding; Inconsistency: even though no PHLF were reported in the HPVE groups across both study, one reported no statistically significant difference compared to PVE while the other one found one (p=0.012); Imprecision: two retrospective studies included with small sample size (n=111).
Disease progressionB	HPVE: 97 PVE: 99 (k=3)	Peritoneal carcinomatosis 0% to 9.7% Intrahepatic progression 0% to 13.5%	Peritoneal carcinomatosis 0% to 2.8% Intrahepatic progression 0% to 9.8%	⨁◯◯◯ Very low	RoB: Lack of allocation concealment and blinding; Inconsistency: results of the three studies had the same trend. However, four patients in the PVE group were not counted as authors didn't specify the reason for ineligibility. The trend **would change** if they had been ineligible due to disease progression.
Insufficient hypertrophyB	HPVE: 97 PVE: 99 (k=3)	Volume: 0% Function: 3.4%	Volume: 2.8% to 4.9% Function: 9.1%	⨁⨁◯◯ Low	RoB: Lack of allocation concealment and blinding; Inconsistency: results of the three studies had the same trend. Four patients in the PVE group were not counted as authors didn't specify the reason for ineligibility. The trend **would not change** if they had been ineligibile due to insufficient hypertrophy.
Safety					
Postoperative mortality **(30-90 day)**	HPVE: 103 PVE: 83 (k=5) [A]	Comparative studies: 0% to 12.2% Case series: 10.0% to 11.1%	Comparative studies: 3.1% to 6.5% Case series: NA	⨁◯◯◯ Very low	RoB: Lack of allocation concealment and blinding; Inconsistency: no death was reported in two of three comparative studies, while the other one stated 12% in HPVE group died (no statistical difference compared to PVE (6.5%)). The two case series, both with small sample size, also reported one death each.
Post-embolisation: major AEs	HPVE: 121 PVE: 99 (k=5) [A]	Comparative studies: 0% Case series: 0%	Comparative studies: 0% to 5.6% Case series: NA	⨁⨁◯◯ Low	RoB: Lack of allocation concealment and blinding.
Post-embolisation: surgical- or device-related AEs	HPVE: 121 PVE: 99 (k=5) [A]	Comparative studies: 5.4% to 20.7% Case series: 8.3% to 16.6%	Comparative studies: 2.4% to 13.6% Case series: NA	⨁◯◯◯ Very low	RoB: Lack of allocation concealment and blinding; Inconsistency: Comparative studies: two studies seemed to have more surgical-related AEs in HPVE group compared to PVE, while no difference in number was reported in the last one; Case series: same trend in number of AEs reported.
Postoperative: major AEs	HPVE: 103 PVE: 83 (k=5)[A]	Comparative studies: 3.7% to 20% Case series: 11.1% to 70.0%	Comparative studies: 9.7% to 31.0% Case series: NA	⨁◯◯◯ Very low	RoB: Lack of allocation concealment and blinding; Inconsistency: Comparative studies: less major AEs seemed to occur in HPVE group compared to PVE in two studies, while the last one reported a higher percentage; Case series: more AEs were reported in one study (n=seven) compared to the other one (n=one, cause: death)

Abbreviations: AE – adverse events; HPVE – hepatic and portal vein embolisation; NA – not applicable; PHLF – post-hepatectomy liver failure; PVE – portal vein embolisation; RoB – risk of bias

Notes: Crude pooling of event counts were conducted for each outcome. No statistical comparisons between HPVE and PVE were made

Comments: A = Three studies are retrospective comparatives and two are case series.

B = In PVE group, four other patients were also ineligible for resection due to contraindication at laparotomy – no reason mentioned, and therefore were not taken into account in the results here.

6 Discussion

HPVE (simultaneous or sequential PVE and HVE) is a new strategy to promote hypertrophy of the FLR prior to major hepatectomy and reduce subsequent AEs to increase the number of patients able to undergo resection, including in patients who remain unsuitable for hepatectomy after PVE alone (20-30% of patients) [7, 19, 22, 39-43]. Although other techniques, including ALPPS, radioembolisation, two-stage hepatectomy, portal vein ligation, as well as combination treatments (such as TACE + PVE), exist to increase functional resectability, PVE remains the first-line option for patients with a small FLR [7, 26, 33]. Indeed, the evidence base reflected this, with PVE being the only comparator used in the available literature.

HPVE fördert Hypertrophie der künftigen Restleber vor Hepatektomie

Komparator: PVE als Erstlinien-Therapie

This report aimed to assess the clinical effectiveness and safety of HPVE in comparison to PVE in patients needing hepatic hypertrophy prior to major hepatectomy. The main outcomes of interest comprised patient-relevant and clinical outcomes, such as PHLF, ineligibility for resection, and 30- or 90-day mortality.

Effektivität und Sicherheit: HPVE vs. PVE

6.1 Summary of evidence

A total of five studies met the PICO criteria for inclusion, comprising three comparative retrospective studies (published in 2019 and 2020) [45, 47, 49] and two prospective case series (published in 2009 and 2021) [63, 64].

5 Studien eingeschlossen: 3 kontrollierte Studien, 2 Fallserien …

No RCTs or prospective non-randomised comparative studies were identified in the literature searches.

Overall, 196 patients were enrolled in the comparative studies assessing the use of HPVE (n=97 patients) compared to PVE (n=99 patients). An additional 24 patients were included in the case series studies, resulting in a total of 120 patients considered for the safety assessment of HPVE. After embolisation, not all patients were able to undergo the planned resection (n=34, 15.5%), due mainly to either disease progression or insufficient hypertrophy. Overall, 103 (HPVE) and 83 (PVE) patients were included for the assessment of postoperative safety outcomes.

… mit gesamt 120 Patient*innen

in 16 % Resektion nach Embolisation unmöglich

Simultaneous HPVE was assessed by all the included studies [45, 47, 49, 63], except for one which performed HVE one to two weeks after PVE in patients whose FLR-V remained <40% of the TLV [64]. According to the literature, simultaneous HPVE is the preferred procedure to avoid an additional waiting period between PVE and HVE operations, thereby reducing the chance of tumour growth before resection.

simultane HPVE (4 Studien), sequenziell PVE-HVE (1 Studie)

The population included in this report is in accordance with the potential patients who could use HPVE before a major hepatectomy (mainly males, age >60 years old, with colorectal liver metastases). However, the potential population could be larger than the one studied here, especially when considering patients with chronic liver diseases, or patients with prior liver interventions or chemotherapy. Furthermore, no applicability issues were raised from the geographical setting of the included studies. The main studies have been conducted in healthcare systems that is comparable to Austria (i.e. France).

Hauptstudienpopulation: Männer, >60 Jahre mit kolorektaler Lebermetastase

heterogene Ein-/ Ausschlusskriterien

Lebermetastasen als Haupttumorart (nach Gallengangskarzinom)

In the inclusion criteria of two of the five studies [45, 49], a normal liver could be included only if the FLR was <25%, while for a diseased liver it would be FLR <35-40%. Patients with an FLR <30-45% without any distinction of the liver background status were included in all the other studies [47, 63, 64]. Moreover, three studies excluded patients with a chronically diseased liver, but included patients receiving chemotherapy before embolisation [45, 47, 63]. The main tumour type found was liver metastases (n=112, 50.9%), followed by cholangiocarcinoma (n=29, 13.2%).

Follow-up zwischen 28 Tagen und 20 Monaten

zu kurz für onkologische Endpunkte

The follow-up time for the three comparative studies was three months after surgery [45, 47, 49], while it varied between 28 days to 20 months in the two case series [63, 64]. Only one patient in all studies was lost to follow-up [64]. The outcomes and timing of the included studies reflect the most important benefits and harms of the procedure. However, if patients' cancer-related outcomes would be of interest (e.g. overall survival), longer follow-ups would be needed.

PHLF: s.s. (1/3 Studie)

unmögliche Leberresektion aufgrund Krankheitsfortschritt oder unzureichender Restleber-Hypertrophie (3/3 Studien)

It should be noted that in the comparative studies, more patients in HPVE group underwent a more aggressive right hepatectomy, including segment IV and sometimes segment I. PHLF and ineligibility for resection due to disease progression or insufficient hypertrophy were the two clinical effectiveness outcomes considered *crucial* to derive a recommendation for which outcome data was available. No evidence on longer-term patient-relevant oncological outcomes was identified. Two comparative studies reported on PHLF. PHLF was reported with a statistically significant difference in one study (HPVE 0% vs PVE 21.9%, p=0.012) [45]; however, this result contrasted with the other study, in which no patients experienced PHLF after either HPVE or PVE [47]. Authors explained this uncommon rate by the fact that resection was only pursued when FLR-F was above the safe threshold (i.e., 2.69%/min/m^2 or 3.23%/min/m^2, depending on the FLR venous outflow and/or in the case of expected large resection) [47]. Disease progression after embolisation, discovered either before or at the time of surgery, was the main reason for resection ineligibility across the three comparative studies, occurring in 0-13.5% and 0-9.8% of patients after HPVE and PVE, respectively [45, 47, 49]. In addition, insufficient FLR hypertrophy (increase in FLR-V or FLR-F) was mentioned in 0-3.4% of patients after HPVE and in 2.8-9.1% after PVE. In one study, an additional four (9.8%) patients presented with a contraindication for resection at the time of surgery (reason not specified) after PVE.

The three comparative studies consistently reported HPVE to be associated with a significantly improved outcome in comparison to PVE with respect to the important but not *crucial* outcome of the degree of hypertrophy.

Mortalität: nicht s.s. (2/3 Studien)

2 Todesfälle (2/2 Studien)

operationsbedingte (5/5 Studien) und schwere (1/5 Studie) unerwünschte Ereignisse: nicht s.s.

Patient safety outcomes *crucial* to derive a recommendation were 30- or 90-day mortality, morbidity (serious AEs or specific hepatobiliary complications), and surgical- or device-related AEs. In two of the three comparative studies, differences in 90-day mortality between HPVE and PVE groups were not statistically significant (HPVE 0% vs PVE 3.1%, p=1; HPVE 12% vs PVE 6.5%, p=0.228) [45, 49], while statistical significance was not reported in the third study (HPVE 0% vs PVE 5%, p=NR) [47]. The two case series reported one non-procedure-related death each [63, 64]. All five studies reported surgical- or device-related AEs after embolisation, at rates of between 5.4-20.7% (HPVE) vs 2.4-13.6% (PVE) group in the comparative studies and 8.3-16.6% (HPVE) in the case series. Non-target embolisation was the main surgically-related AE reported [45, 49, 63, 64]. Major complications after an embolisation were assessed in all five studies, but only one study reported two Clavien-Dindo

grade ≥III events (i.e. serious AEs) in the PVE group with no significant difference [45]. Serious AEs after resection (Clavien-Dindo ≥III) were reported in 3.7-20.0% of patients in HPVE group, and in 9.7-31.0% of patients in the PVE group for comparative studies [45, 47, 49], while in the case series, serious AEs after resection ranged from 11.1-70.0% [63, 64]. One comparative study reported hepatobiliary complications as a composite outcome, finding no statistically significant difference between groups [49]. A second comparative study found no statistically significant difference with respect to biliary leak, ascites, or intra-abdominal collection [45].

systematische Übersichtsarbeit zu HPVE

A systematic review on the topic of HPVE, published in 2019 (the date of the literature search was July 2018), included six case series or case reports on simultaneous HPVE or sequential PVE-HVE [40]. Authors concluded that HPVE could induce hypertrophy of the FLR and allow surgery in patients initially judged unsuitable for resection. Authors were limited to narrative reporting due to low study quality and a low number of patients. A narrative review of the HPVE technique has also recently (2021) been published, although this study lacks a rigorous systematic review methodology [50]. Authors concluded the available data demonstrate that HPVE is associated with similar rates of morbidity and mortality as PVE but induces faster and more extensive hypertrophy, which increases resectability compared to PVE. Nonetheless, it is subsequently noted that future RCTs are needed to determine the true benefit of HPVE [50].

3 Vergleichsstudien

Since the time of the last systematic review on HPVE [40], three comparative studies on the technique (compared to PVE) have been published [45, 47, 49]; two of which were described in the recent narrative review [50]. These provide preliminary evidence that HPVE may be superior to PVE with regard to the degree and speed of hypertrophy whilst being as safe as PVE. Nonetheless, the quality and GRADE assessments undertaken as part of our systematic review methodology show that the available evidence remains to be of a low to very-low quality, indicating further research is required before a recommendation can be made, as was similarly concluded by the existing narrative and systematic reviews [40, 50].

6.2 Quality of evidence

(sehr) niedrige Qualität der Evidenz

Overall, the quality of evidence ranged from very low to low, considering clinical effectiveness and patient safety outcomes (see Quality of evidence and Table A-3 to Table A-6 in the Appendix). The design (observational: retrospective and case series) of all included studies highly impacted the level of evidence. RoB was assessed as moderate for the three comparative studies and low for the two case series. Bias due to confounding, including blinding and patient selection, were the two main reasons for downgrading the studies, as well as missing data in one comparative study [47]. Moreover, another RoB was considered in one comparative study in relation to its inclusion criteria [45] RoB in GRADE was assessed as serious for all the outcomes due to the fact comparative studies were ranked as moderate and used to evaluate all the crucial outcomes. The overall strength of evidence for the effectiveness and safety of HPVE in comparison to PVE ranged from very low to low.

niedriges bis moderates Verzerrungsrisiko

hohes Verzerrungsrisiko in GRADE in allen Endpunkten

Effektivität: Inkonsistenz und Ungenauigkeit in Endpunkten

For clinical effectiveness outcomes assessed in the three comparative studies, two other factors also downgraded the level of evidence. Even though no meta-analysis was performed, inconsistency among the results was found (for PHLF and disease progression outcomes), as well as imprecision (for PHLF) due to a low number of patients enrolled (n=111) and a low number of studies reporting the outcome (n=two).

Sicherheit: Inkonsistenz in Endpunkten

Stichprobengröße

Concerning patient safety outcomes analysed in the five included studies, inconsistency among the results was also found in three of four outcomes (postoperative mortality, surgical-related AE after embolisation, and major AE after resection). Moreover, the two case series used for safety outcomes enrolled a limited number of patients (n= twelve in each). These limitations are probably due to the novelty of the technique.

6.3 Evidence gaps and ongoing studies

nicht alle potenziellen Populationen vertreten

An evidence gap we found when assessing the data of the five included studies is that not all the potential subpopulation groups were represented. Indeed, patients with Klatskin tumours and underlying liver diseases, such as cirrhosis, fibrosis, were the most excluded populations. It could be explained by the fact that liver regeneration is known to be impacted by chronic liver diseases [7, 38, 39]. More evidence regarding these subpopulations is needed, including for patients with chronic liver diseases (e.g. fibrosis, cirrhosis), or more complex carcinoma (e.g. Klatskin tumour).

Evidenz bezüglich Subpopulationen nötig

künftige Studien: HPVE bei Leberzellenkarzinom vs. kolorektalen Lebermetastasen

Furthermore, future research should investigate the potential differences in the effectiveness of HPVE between patients with HCC and those with colorectal liver metastases. Indeed, most HCC occurs in patients with a cirrhotic or semi-cirrhotic liver which is known to impact the liver's capacity for regeneration and, therefore, the likelihood of treatment success. In contrast, colorectal liver metastases usually occur in otherwise healthy livers where procedures to induce hypertrophy are more likely to succeed. Functional assessments, such as scintigraphy, should be systematically performed in the future in order to have an overview of the liver (volume and function). Moreover, the benefits of HPVE need to be assessed when used in conjunction with other technologies known to influence liver regeneration, such as chemotherapy.

2 laufende Studien:

1 multi-zentrische RCT

1 multi-zentrische unkontrollierte Studie als Basis für weitere RCT

Two relevant ongoing open-label trials have been identified, including one multi-centre RCT (HYPER-LIV01, comparing HPVE to PVE) and a multi-centre single-arm feasibility evaluation (DRAGON 1), intended as the base for a second RCT (DRAGON 2, comparing HPVE to PVE) (see Table A-8 in the Appendix). The estimated primary completion date of the ongoing RCT (HYPER-LIV01) was October 2021. The start date of DRAGON 2 was planned for 2021, however, it is not yet registered on a clinical trials registry. The estimated primary completion data for DRAGON 1 is May 2022. – These ongoing and upcoming trials could potentially influence the effect estimates considerably.

6.4 Limitations

Studiendesigns

This systematic review results should be interpreted in light of its limitations. The main limitation of this report is that the evidence is limited to observational studies, and the only available comparative evidence is retrospective. 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.

graue Literatur

Although the present report followed a transparent and systematic methodology, including a systematic literature search according to the PICO scheme, it also has a few weaknesses. These include an absence of extensive grey literature searches, such as unpublished reports (i.e. from manufacturers, thesis, etc.), speciality society, or hospital websites. Secondly, language was restricted to English only, meaning studies published in national journals may have been missed. Nevertheless, it is unlikely that additional data would have changed the conclusion that new evidence is needed to assess the comparative effectiveness and safety of HPVE.

6.5 Conclusion

Evidenz unzureichend

Based on the limited evidence we found – three retrospective comparative studies and two prospective case series – no conclusion can be made whether HPVE leads to better outcomes than the first-line comparator PVE.

simultane HPVE bevorzugt

Simultaneous HPVE seems to be the preferred technique among the included studies and literature in comparison to sequential PVE-HVE, as the delay for surgery is reduced, and it can be performed as a dual procedure instead of two separate procedures.

Hypertrophie der Restleber: größer und schneller bei HPVE als PVE

However, considering the results assessed in this report, FLR hypertrophy seems to be greater and faster with HPVE compared to PVE, whereas it didn't appear to improve the unresectability due to disease progression, or reduce the time between embolisation and resection. HPVE seems to be as safe as PVE, although no formal statistical analyses were performed.

laufende Studien abwarten

The results of the two ongoing trials (HYPER-LIV01 and DRAGON-1, completion date April and May 2022), as well as the results of the upcoming one (DRAGON-2, planned start date 2021), will provide more clarifications on the effectiveness and safety of HPVE.

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:

Based on the limited evidence we found – three retrospective comparative studies and two prospective case series – no conclusion can be made whether HPVE leads to better outcomes than the first-line comparator PVE. Thus, the current evidence is not sufficient to prove that the assessed technology HPVE is more effective and safe than the comparator PVE.

Evidenz unzureichend

New study results from the two ongoing trials will potentially influence the effect estimate considerably. The re-evaluation is recommended in 2023 if evidence from the ongoing trials becomes available.

Neubewertung nicht vor 2023 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Portal and hepatic vein embolisation: Results from non-randomised comparative trials

Author, year	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
Country	France	France	France
Sponsor	None	NR	None
Intervention/Product	LVD	RASPE	BE
Comparator	PVE	PVE	PVE
Study design	Single-centre retrospective non-randomised comparative study	Single-centre retrospective non-randomised comparative study	Single-centre retrospective non-randomised comparative study
Number of pts	Total: 51 (LVD:29; PVE:22)	Total: 73 (RASPE:37; PVE:36)	Total: 72 (BE:31; PVE:41)
Inclusion criteria	Patients referred for liver preparation before major hepatectomy with small FLR (volume <30% of TLV or function [99mTc-mebrofenin clearance rate] <2.69%/min/m2) An additional 20% functional margin was considered for planned resection at risk.	Patients eligible for right liver resection (extended or not extended to segment IV) needing preoperative FLR hypertrophy (FLR<25% of the normal liver or <35% of the diseased liver, and/or an RLV/BW ratio<0.5). RASPE for patients with FLR <25% PVE for patients with 25<FLR<35%	Indication for pre-operatie FLR hypertrophy: FLR <25% (normal liver) or <40%(underlying liver disease) and/or an FLR/bodyweight ratio <0.5%. Patients with Klatskin 2 or 3A extrahepatic cholangiocarcinoma underwent systematic preoperative embolisation. NB: Patients who underwent preoperative PVE or BE between January 2010 and December 2017 qualified for inclusion. PVE was used prior to 2014. From 2014, BE was proposed as an alternative to PVE, initially when the FLR-V anticipated after PVE was insufficient but gradually, because BE was well tolerated, BE was performed in all patients
Exclusion criteria	Lack of baseline 99mTc-mebrofenin SPECT-CT or follow-up data for the first 3 weeks after liver preparation; cirrhosis; Klatskin tumour; and two-stage hepatectomy	Patients with liver fibrosis or cirrhosis	Patients with chemoembolisation plus embolisation
Age of patients (yrs) Median (range)	63 (26-79) LVD: 62 (26-79) PVE: 66 (45-79), p=0.219	RASPE: 64.41 (61-71) PVE: 60.92 (51-72), p=0.340	BE: 66 (CI:55-70) PVE: 63 (CI:60-68), p=0.562
Gender, Male, n (%)	37 (LVD:21 [72.4%]; PVE: 16 [72.7%]), p=1	51 (RASPE: 25 [68%]; PVE: 26 [72%]), p=0.903	44 (BE: 16 [52%]; PVE: 28 [68%]), p=0.222
BMI kg/m^2 Median (range, IQR or CI)	26.3 (R: 16-35.2) LVD: 26.3 (17.6-34.5) PVE: 25.1 (16-35.2), p=0.108	RASPE: 25.41 (IQR: 7) PVE: 25.54 (IQR: 6), p=0.900	BE:24 (CI:23-27) PVE: 24 (CI: 23-29), p=0.564
Tumour type (n)			
Liver metastases	39 (LVD: 22; PVE:17)	43 (RASPE: 23; PVE:20)	18 (BE:18; PVE:NR)

Author, year	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
ICC	7 (LVD: 4; PVE:3)	14 (RASPE: 7; PVE:7)	2 (BE:2; PVE:NR)
HCC	3 (LVD: 2; PVE:1)	8 (RASPE: 4; PVE:4)	5 (BE:5; PVE:NR)
Other[a]	2 (LVD: 1; PVE:1)	5 (RASPE: 2; PVE:3)	6 (BE:6, PVE:NR) NB: data for PVE group is missing from the publication
Chemotherapy (n)	Number of patients on chemotherapy: 42 of 51	Number of preoperative chemotherapy treatments: RASPE: mean: 4.486 (SD: 0.7369) PVE: mean: 4.0 (SD: 0.666)	NR
Background liver status			
Cirrhosis, n (%)	LVD 0(0), PVE 0 (0); excluded	RASPE 0(0), PVE 0 (0); excluded	BE 3(10), PVE 4(10)
NASH, n (%)	NA	NA	BE 9(29), PVE 11(27)
Fibrosis, n (%)	NA	RASPE (0), PVE 0 (0) excluded	NA
Planned (or performed) surgery (n)	Planned surgeries:	Surgeries performed:	Surgeries performed:
RHH	23 (LVD: 13; PVE:10)	29 (RASPE: 10; PVE: 19)	8 (BE:8; PVE:NR)
RHH + segment I or IV	26 (LVD: 15; PVE:11)	NA	6 (BE:6; PVE:NR)
RHH + segment I + IV	2 (LVD: 1; PVE:1)	NA	9 (BE:9; PVE:NR)
RHH+ segment IV ± I	NA	35(RASPE: 22; PVE: 13)	NA
ALPPS	None	None	3 (BE:2; PVE:1)* * due to very high intraoperative portal pressure NB: data for PVE group is missing
Follow-up (days or months)	Post-embolisation: 21 days Postoperative: 90 days	Post-embolisation: 30 days (morbidity and mortality); assessment of FLR: median 31 days (21-40) after embolisation Postoperative: 90 days	Post-embolisation volumetric analysis at mean of 27 and 26 days in PVE and BE groups Postoperative: 3 months
Safety outcomes after embolisation			
Loss to follow-up, n (%)	none	none	none
Ineligible for planned hepatic resection n/N (%)	4/51 (7.8%) (LVD: 2; PVE: 2) Disease progression: peritoneal carcinomatosis discovered at surgery: 1 (LVD:1; PVE: 0) Insufficient FLR-F: 3 (LVD:1 ; PVE:2)	9 (RASPE: 5; PVE:4) Disease progression: Intrahepatic progression: 7 (RASPE: 5; PVE: 2) Peritoneal carcinomatosis: 1 (RASPE: 0; PVE: 1) Insufficient hypertrophy of FLR:1 (RASPE: 0; PVE: 1)	16 (BE: 6; PVE: 10) Disease progression: 10 (BE: 6; PVE:4) Discovered at preoperative imaging: 7 (BE: 3; PVE: 4) Peritoneal carcinomatosis discovered at surgery: (BE: 3; PVE: 0) Contraindication at laparotomy reason NR: 4 (BE: 0; PVE:4) Insuficient FLR: 2 (BE: 0; PVE:2), p=0.212
Time between embolisation and resection	Median (range), days LVD 32 (22-46), PVE 36 (22-55), p=0.12	Median (range), days RASPE 36 (16-47), PVE 44 (21-78) Mean, SD RASPE 36.25 ± 2.742, PVE 44.68 ± 4.879, p=0.144	NR

Author, year	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
Technical success rate for embolisation %	LVD: 100% PVE: 100%	RASPE: 100% PVE: 100%	NR
Recurrence, n/N (%)	NR	NR	NR
Surgically- or device-related AE, n/N (%)	LVD: 6/29; PVE: 3/22 Minor peri-hepatic hematoma: 3 (LVD: 2; PVE: 1) Transient grade 1-2 asthenia: 6 (LVD: 4 ; PVE: 2)	RASPE: 2; PVE:2/36 Erractic embolisation in the segmental branch: 3 (RASE: 1; PVE: 2) Hemoperitoneum: 1 (RASPE: 1; PVE: 0)	BE: 3/31; PVE: 1/41 Unintentional embolisation of the middle hepatic vein instead of RHV: 1 (BE: 1; PVE: 0) High intraoperative portal pressure at surgery: 3 (BE: 2; PVE: 1)
Findings from histologic assessment Sinusoidal dilatation	LVD: 18/27 (66.7%); PVE: 9/20, (45.0%), p=0.21*		
Atrophy of centro- and medio-lobular hepatic plates	LVD: 18/27 (66.7%); PVE: 8/20 (40%), p=0.07*		
Haemorrhage and necrosis	LVD: 13/27 (48.1%); PVE: 7/20 (35%), p=0.37* NB: * represent the total number of patients who had resection		
Underlying diseased liver type	NR		NR
Moderate and severe sinusoidal obstruction syndrome		RASPE:22/32 (69%); PVE:20/32 (63%)	
Hepatic steatosis >30%, grades 2-3		RASPE:4/32 (12%) ; PVE:3/32 (9%)	
Major AE, n/N (%), after Embolism	0/51	2/73	0/72
Clavien-Dindo classification >III n/N		RASPE 0/37; PVE 2/36, p=0.493	
Minor AE, n/N (%), after Embolism Clavien-Dindo classification I-II, n/N		RASPE 37/37; PVE 34/36	0/72
Pain intensity, after embolisation, VAS	NR		NR
VAS 1-3, n (%)		RASPE 12(32), PVE 14(39), p=0.81	
VAS 4-6, n (%)		RASPE 13(36), PVE 14(39), p=1	
VAS 7-10, n (%)		RASPE 12(32), PVE 8(22), p=0.614	
Post-embolisation blood test results	NR	1 day after procedure, median (range):	1 day after procedure, median (CI):
ASAT, IU/L, median (range)		RASPE 64,5 (39.75-105.50), PVE 46 (33-72), p=0.351	BE 43 (31-82), PVE 45 (32-53), p=0.972
ALAT, IU/L, median (range)		RASPE 68 (37.25-111.50), PVE 47 (31-114), p=0.792	BE 61 (37-105), PVE 57 (40-70), p=0.573
GGT, IU/L, median (range)		RASPE 118.50 (55.25-271), PVE 100 (63-235), p=0.923	NR
PT (%), median (range)		RASPE 94 (78-100), PVE 91 (74-100), p=0.431	BE 84 (76-94), PVE 89 (80-99), p=0.204
Bilirubin, mg/dL, median (range)		RASPE 8 (6-10.75), PVE 9(8-15), p=0.141	BE 14(9-20), PVE 16 (10-35), p=0.351

Author, year	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
Hospital stay after embolisation, median days, (range)	2 (2-5)	RASPE: 1.43 (1-5), PVE: 1.86 (1-10) p=0.192	All patients were discharged the following day without complication
Efficacy outcomes after embolisation			
% hypertrophy of the FLR	Median (min to max) (%) Day 0-7: LVD 37.8 (−4.1 to 88.3), PVE 28.7 (−20.4 to 90.2), p=0.23 Day 0-14: LVD 50 (−4.4 to 90.6), PVE 14.2 (−23.5 to 58.6), p=0.002 Day 0-21: LVD 52.6 (1 to 175.6), PVE 18.6 (−10.7 to 102.2), p=0.001 NB: volume and functional evaluations were missing for 12/51 (23.5%), 15/51 (29.4%) and 13/51 (25.5%) patients at days 7, 14, and 21. Missing data were handled using multiple imputation analysis.	Median (range) RASPE 61.18% (23, 18-201, 56) PVE 28.98% (9.31-61.23) p <0.0001	Mean (± SD) BE: 51.2% (±41.7%), PVE: 31.9% (±34%), p=0.018 For segment 4 only: Median [CI] BE: 12% (-10-43%), PVE: 16% (-4-55%), p=0.707
FLR-V	mL, median (range) At baseline LVD: 484 (233-805), PVE: 542 (236-1,119) p=0.285	mL, median (range) Pre-embolisation RASPE: 387 (200-623), PVE: 468 (253-945) p=0.0082 Post-embolisation RASPE: 611 (389-979), PVE: 636.5 (326-1142) p=0.867	median, cc Pre-embolisation BE 394 (262-478), PVE 348 (266-547), p=0.43 Post-embolisation BE 527 (416-662), PVE 487 (327-612), p=0.794 For segment 4 only: Pre-embolisation BE 244 (187-295), PVE 221(171-333), p=0.743 Post-embolisation BE 284 (225-337), PVE 272 (225-334), p=0.635
FLR-F	%/min/m2, median (range) FLR-F at baseline LVD: 1.9 (1.26-2.5), PVE: 2.59 (1.3-3.13), p<0.001 Change in FLR-F (%), median (min to max) Day 0-7 LVD 54.3 (−2 to 105.6), PVE 23.1 (−16 to 86.4), p=0.02 Day 0-14 LVD 56.1 (−5.2 to 94.7), PVE 17.6 (−20 to 68.9), p=0.006 Day 0-21 LVD 68.2 (25.4 to 121.4), PVE 29.8 (1.1 to 63.9), p<0.001 NB: volume and functional evaluations were missing for 12 (23.5%), 15 (29.4%) and 13 (25.5%) patients at days 7, 14 and 21. Missing data were handled using multiple imputation analysis.	NR	NR

Author, year	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
FLR/TLV % median (range)	Baseline: LVD: 22.6 (16.6-37.7), PVE: 27.4 (13.7-47.7)p=0.175	Pre-embolisation RASPE: 22,91 (16.55-32.15) PVE: 31.03 (18.33-38.95), p=0.0001 Post-embolisation RASPE: 39.89 (30.64-52.92) PVE: 39.49 (24.11-53.86), p=0.460	The increase in the FLR/TLV ratio after compared to before embolisation: BE:10% (±6%), PVE: 7.5% (±5%), p=0.047
Kinetic growth rate mean	NR	NR	BE 19%/week (±18%/week), PVE 8%/week (±13%/week), p=0.026
Change in TLV (%), median (min to max)	Day 0-7 LVD 11.1 (−5.1 to 54.3), PVE 15 (−34.5 to 52.5), p=0.57 Day 0-14 LVD 11.8 (−13.6 to 46.7), PVE 1.2 (−21.2 to 64), p=0.07 Day 0-21 LVD 12.9 (−12.7 to 66), PVE −1.5 (−16.3 to 36), p=0.03 NB: volume and functional evaluations were missing for 12 (23.5%), 15 (29.4%) and 13 (25.5%) patients at days 7, 14, and 21. Missing data were handled using multiple imputation analysis.	NR	NR
Total liver function	Baseline (%/min/m^2) LVD: 8.52 (5.67-15.46), PVE: 9.34 (5-14.9) Change from baseline (%), median (min to max) Day 0-7 LVD −12.2 (−35.7 to 15.2), PVE −3.7 (−30.8 to 49.8), p=0.08 Day 0-14 LVD −14 (--32.8 to 13.9), PVE 0.1 (−41 to 35), p=0.15 Day 0-21 LVD −15 (−33.5 to 36.5), PVE −9.4 (−24.8 to 11.2), p=0.65 NB: volume and functional evaluations were missing for 12 (23.5%), 15 (29.4%) and 13 (25.5%) patients at days 7, 14, and 21. Missing data were handled using multiple imputation analysis.	NR	NR
R0 resection rate	NR	RASPE 31/32, PVE 30/32	NR
Hospital stay after resection, median days	NR	RASPE 7 (range:4-26), PVE 8 (range:4-39), p=0.33	BE 19 (CI 14), PVE 17 (CI 8), p=0.823
Safety outcomes after surgery			
Major AE, n/N (%), p, after surgery Clavien-Dindo ≥ IIIA	LVD: 3/27 (3.7%); PVE: 3/20 (15%)	RASPE:6/32 (19%) ; PVE:10/32 (31%)	BE: 5/25 (20.0%); PVE:3/31 (9.7%)
Specified AEs, n/N (%), p, after surgery			
Biliary leak	NR	RASPE:3/32 (9%), PVE:1/32 (3%), p=0.614	NR

Author, year	Guiu et al. [47]	Laurent et al. [45]	Le Roy et al. [49]
Ascites	NR	RASPE:2/32 (6%), PVE:2/32 (6%), p=1	NR
Intra-abdominal collection	NR	RASPE: 2/32 (6), PVE: 3/32 (9); p=1	NR
Liver failure	LVD: 0/27; PVE: 0/20	RASPE:0/32 (0%), PVE:7/32 (21.9%), p=0.012	NR
Hepatobiliary complications**	NR NB: PHLF was assessed according to the "50-50" criteria	NR NB: PHLF was defined as an increased international normalized ratio (INR) with hyperbilirubinemia ≥ 5 days after surgery; classified as grade A-C as proposed by the International Study Group of Liver Surgery	BE: 9/25, PVE:9/31** NB: **hepatobiliary complications included postoperative ascites, encephalopathy, jaundice, pro-thrombin time (PT) value below 50% and a serum bilirubin concentration exceeding 50 mmol/l on POD 5 ("50-50 criteria"), and/or by a postoperative peak bilirubin value of at least 120 mmol/l on POD 7, and/or by grade C liver failure as defined by the International Study Group of Liver Surgery
Minor AE, n/N (%), p, after surgery Clavien-Dindo classification (I and II)	NR	RASPE:26/32; PVE:22/32	BE: 10/25; PVE:9/31
Blood lost, mL mean, p		RASPE 593.5 ± 90.93 ; PVE 595 ± 72.65, p=0.995	BE 1310 (CI1374), PVE 972 (CI655), p=0.688
Post-surgery blood test results	POD 5:	POD 5:	NR
ASAT, IU/L, median (range)	NR	RASPE 55(41-360), PVE 72 (51-329) p=0.241	
ALAT, IU/L, median (range)	NR	RASPE 112 (84-173), PVE 132 (104-252), p=0.170	
GGT, IU/L, median (range)	NR	RASPE 209 (103-1172), PVE 234 (152,5-871), p=0.760	
Bilirubin IU/L, median (IQR or range) µmol/L	LVD 34 (17-43), PVE 38 (18-44), p=0.38	RASPE 21 (14-41), PVE 24 (18-159), p=0.322	
PT % median (IQR or range)	LVD 67 (56-86), PVE 65 (54-80), p=0.56	RASPE 89 (52-100), PVE 81 (27-100), p=0.028	
Postoperative mortality, n/N (%)	1/47	1/64	5/56
NB: 90-day/3-month mortality	LVD: 0/27 (0%), PVE:1/20 (5.0%), p=NR	RASPE: 0/32 (0%), PVE: 1/32 (3.1%), p=1	BE: 3/25 (12.0%), PVE:2/31 (6.5%), p=0.228

Abbreviations: ALAT – alanine aminotransferase, ASAT – aspartate aminotransferase, BE – bi-embolisation, BMI – body mass index, CI – confidence interval, FLR-F – function of the future liver remnant, FLR-V – volume of the future liver remnant, GGT – gamma-glutamyl transferase, HCC – hepatocellular carcinoma, ICC – intrahepatic cholangiocarcinoma, IQR – interquartile range, LVD – Liver venous deprivation, NA – not applicable, NASH – non-alcoholic steatohepatitis, NR – not reported, POD – postoperative day, PT – prothrombin time, PVE – portal vein embolisation, R – range, RASPE – radiological simultaneous porto-hepatic vein embolisation, RHH – right hemi-hepatectomy, SD – standard deviation, TLV – total liver volume, VAS – visual analogue scale

Notes: [a] Other: epithelioid hemangioendothelioma, liver adenoma, neuroendocrine tumours, extrahepatic cholangiocarcinoma

Table A-2: Portal and hepatic vein embolisation: Results from observational studies

Author, year	Ghosn et al. [63]	Hwang et al. [64]
Country	USA	South Korea
Sponsor	Post doc research fellowship from General Electric, Olympus medical, RSNA (Scholar Grant), SIR (Ernest Ring Academic Development), Guerbet Group, ThompsonFoundation, advisory board member in Management of HCC for Genentech and AstraZeneca, co-founder of Claripacs, LLC, GE Healthcare, Bayer, Steba Biotech, Terumo, research grant and speaker fees from Society of Interventional Oncology, which were sponsored by Guerbet. Investor in Labdoor, Qventus, CloudMedx, Notable Labs, and Xgenomes, USProv. Appl. No. 62/817,116 and 62/754,139 and on U.S. Patent 8233586; stockholder for Amgen, consultant for Accurate Medical, speaker fees from Vindico Medical Education; research grant from Amgen; research grant with GE Healthcare, Johnson & Johnson, and AngioDynamics; shareholder in Johnson & Johnson; consultant for Varian, Microbot.	NR
Intervention/Product	LVD	Sequential PVE – HVE
Comparator	None	None
Study design	Prospective	Prospective
Number of pts	12	12
Inclusion criteria	■ LVD prior to right hepatectomy or right trisectionectomy with an FLR <35-40% of TLV. ■ Insufficient FLR predicted after PVE (Mise et al. nomogram). *1 or more of the following: 2 or more chemotherapy lines, more than 6 cycles of chemotherapy, intra-arterial chemotherapy through a HAIP in addition to systemic chemotherapy, prior radiation therapy to the liver, BMI > 30 kg/m^2	■ Indications for right PVE prior to right hepatectomy or more extensive liver surgery for hepatobiliary malignancy, small FLR less than 40% of TLV. ■ Perihilar cholangiocarcinoma patients: decompression of the entire biliary system first, then serum total bilirubin level lower than 5 mg/dL. ■ Indications for HVE: if FLR still < 40% of TLV 1-2 weeks after PVE. Exception: patients with serious comorbidities or planning for hepatopancreatoduodenectomy: FLR < 45% of TLV
Age of patients (yrs) Mean (SD)	55.5 ± 11.8	60.5 ± 10.3
Gender, n (woman/man)	2/10	2/10
Cancer type, n	Colorectal liver metastasis, 12	perihilar cholangiocarcinoma, 8 HCC, 3 ICC, 1
Background liver status, n Cirrhosis	0	2
Prior liver intervention n (%) Surgery Radiotherapy	4 (34) 2 (17)	NR
Chemotherapy (pts n)	12	NR
Hepatic arterial infusion pump, n (%)	6 (50)	NR
Follow-up (months), range	NR	28 days – 20 months
Loss to follow-up, n (%)	0 (0)	1/12 (8.3)

Author, year	Ghosn et al. [63]	Hwang et al. [64]
Ineligible for planned hepatic resection	2 Disease progression (n=1); insufficient FLR ratio (n=1)	3 Error in embolisation location and disease progression (n=1); insufficient FLR (n=2*) NB: * In one patient with insufficient FLR, resection was later performed 17 months after HVE. This patient underwent TACE in the interim
Recurrence, n (%)	NR	1 before resection, 2 after
Waiting time between PVE and HVE, days	NA (simultaneously)	13.5 ± 4.2 NB: after excluding 1 patient who required a 2-month wait (case 5)
Waiting time from embolisation to surgery mean, days, range	39 ± 7.5, NR	22.1 ± 8.1, 14 – 38 (median 21) NB: this is for 9 patients undergoing pre-planned operations. An additional one patient underwent right hepatectomy 17 months after HVE, having TACE in the interim
Major AE after embolisation, n/N (%)	0	0
Minor AE after embolisation, n/N (%)	2/12 (16.6) Right upper quadrant pain requiring morphine (n=2)	5/12 (41.6) Transient symptoms and signs including mild abdominal pain, low-grade fever, nausea
Surgical or device-related AE after embolisation, n/N (%)	2/12 (16.6) Non-target embolisation in segment 2 requiring no intervention (n=1) Bland thrombosis of the proximal right portal vein requiring 30 days anticoagulation therapy (n=1)	1/12 (8.3) MHV was erroneously embolized instead of the RHV; error not detected until 1 week post-procedure on a CT scan
Procedure-related mortality, n/N (%) = LVD	0/12 (0)	0/12 (0)
Postoperative complications after resection (Clavien-Dindo) > Class IIIa n/N (%)	7/10 (70) Postoperative abscess (n=1) (Class IIIa) Leukocytosis requiring percutaneous drainage (n=4) (Class IIIa) Liver failure & acute kidney insuffiiciency (n=1) (Class IVb) Death (n=1) (Class V)	1/9 (11.1) Death (n=1) (Class V) ** denominator reflects patients who underwent planned operations
Postoperative mortality, n/N (%) 30- or 90-day	1/10 (10) NB: authors do not specify the follow-up period. The one reported death occurred one month after surgery.	1/9 (11.1) ** denominator reflects patients who underwent planned operations NB: the one reported death occurred on postoperative day 28; remaining patients alive between 8-20 months follow-up.
Blood loss requiring transfusion, n/N (%)	1/10 (10)	4/9 (44.4) ** denominator reflects patients who underwent planned operations

Abbreviations: AE – adverse events, BMI – body mass index, FLR – future liver remnant, HAIP – hepatic arterial infusion pump HCC – hepatocellular carcinoma, HVE – hepatic vein embolisation, ICC – intrahepatic cholangiocarcinoma, LVD – liver venous deprivation, MHV – middle hepatic vein, NR – not reported; PVE – portal vein embolisation, TACE – transarterial chemoembolisation, TLV – total liver volume.

Notes: LVD and PVE – HVE: both techniques refer to HPVE procedure.

Risk of bias tables and GRADE evidence profile

Internal validity of the included and excluded studies was judged by two independent researchers (DF and MV). In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [66] and in the Guidelines of EUnetHTA [67].

Table A-3: Risk of bias assessment of the non-randomised comparative studies

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Guiu et al. [47]	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate	Missing data but said they obtained same results with imputation
Laurent et al. [45]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate	Said in the discussion there were differences at baseline, but the 'matching process' reduced the bias. No description of what the matching process was though
Le Roy et al. [49]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate	

Table A-4: Risk of bias – study level (case series), see [68]

RoB Domain	Ghosn et al. [63]	Hwang et al. [64]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes
2. Was the study conducted prospectively?	Yes	Yes
3. Were the cases collected in more than one centre?	No	No
4. Were patients recruited consecutively?	Yes	No
5. Were the characteristics of the patients included in the study described?	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	Yes
8. Was the intervention of interest clearly described?	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes
10. Were relevant outcome measures established a priori?	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes
18. Were the adverse events reported?	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes
20. Were both competing interests and sources of support for the study reported?	Yes	Yes
Overall Risk of bias	**Low**	**Low**

Note: the two case series were included for the assessment of patient safety only (i.e. not for efficacy outcomes)

Table A-5: Risk of bias assessment of the seven excluded non-randomised comparative studies

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Chebaro, 2021	Serious	Moderate	Moderate	Serious	Critical	Low	Moderate	Critical	Did not compare baseline characteristics
Hocquelet, 2018	Moderate	Moderate	Low	Low	Serious	Low	Moderate	Serious	Only 12 patients, low statistical power. Baseline characteristics were NS but only looked at age and bilirubin level. No matching.
Mastoff, 2021	Critical	Moderate	Low	Serious	Serious	Low	Moderate	Critical	"Patients with extended tumour load and those who were prone to become inoperable were considered primarily for HPVE." Serious selection bias – no adjustment.
Panaro, 2019	Moderate	Moderate	Low	Low	Serious	Low	Moderate	Serious	Did not compare baseline characteristics
Piron, 2021	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate	Only 12 patients, low statistical power. Did not compare baseline characteristics
Heil, 2021	Serious	Moderate	Low	Moderate	Low	Low	Moderate	Serious	Serious risk of bias due to confounding. Differences at baseline for age, liver status and comorbidity index and no adjustment made to correct for this.
Kobayashi, 2020	Serious	Serious	Low	Low	Serious	Low	Low	Serious	Issues included mixed cancer types at baseline, missing data (those that dropped out before undergoing resection were not reported at all).

Abbreviations: HPVE – hepatic and portal vein embolisation, NS – non-statistical

Table A-6: Evidence profile: efficacy and safety of hepatic and portal vein embolisation

Certainty assessment							Summary of findings			Certainty (Importance)
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HPVE; Range	PVE; Range	Comparative Effect	
Post-hepatectomy liver failure (follow-up: 3 months)										
2	observational studies	serious[a,g]	serious[b,c]	not serious	serious[d]		0%	0% to 21.9%	not estimable	⨁◯◯◯ Very low (Critical)
Unresectable due to disease progression (follow-up: range 21 days to 40 days)[C]										
3	observational studies	serious[a,g]	not serious	not serious	not serious		Peritoneal carcinomatosis 0% to 9.7% Intrahepatic progression 0% to 13.5%	Peritoneal carcinomatosis 0% to 2.8% Intrahepatic progression 0% to 9.8%	not estimable	⨁◯◯◯ Very low[D] (Critical)
Unresectable due to insufficient hypertrophy (follow-up: range 21 days to 40 days)[C]										
3	observational studies	serious[a,g]	not serious	not serious	not serious		Volume: 0% Function: 3.4%	Volume: 2.8% to 4.9% Function: 9.1%	not estimable	⨁⨁◯◯ Low[D] (Critical)
Postoperative mortality (follow-up: range 30 days to 90 days)[A]										
5[B]	observational studies	serious[a,g,h]	serious[c]	not serious	not serious[e]		Comparative studies: 0% to 12.2% Case series: 10.0% to 11.1%	Comparative studies: 3.1% to 6.5% Case series: NA	not estimable	⨁◯◯◯ Very low (Critical)
Major AE after embolisation (follow-up: range 21 days to 1 months)[A]										
5[B]	observational studies	serious[a,g,h]	not serious	not serious	not serious[e]		Comparative studies: 0% Case series: 0%	Comparative studies: 0% to 5.6% Case series: NA	not estimable	⨁⨁◯◯ Low (Critical)
Surgical-related AE after embolisation (follow-up: range 21 days to 1 months)[A]										
5[B]	observational studies	serious[a,g,h]	serious[c]	not serious	not serious[e]		Comparative studies: 5.4% to 20.7% Case series: 8.3% to 16.6%	Comparative studies: 2.4% to 13.6% Case series: NA	not estimable	⨁◯◯◯ Very low (Critical)
Major AE after resection (follow-up: range 3 months to 20 months)										
5[B]	observational studies	serious[a,g,h]	serious[c]	not serious	not serious[e]		Comparative studies: 3.7% to 20% Case series: 11.1% to 70.0%	Comparative studies: 9.7% to 31.0% Case series: NA	not estimable	⨁◯◯◯ Very low (Critical)

Abbreviations: AE – adverse events, HPVE – hepatic and portal vein embolisation, NA – not applicable, PVE – portal vein embolisation

Notes: A = Follow-up of major AE and surgical-related AE are based on the information provided by the three comparative studies. The two observational ones did not specify a follow-up time after embolisation. B = Three studies are retrospective comparative and 2 are case series. C = In PVE group, four other patients were also ineligible for resection due to contraindication at laparotomy – no reason mentioned . D = Disease progression was downgraded compared to insufficient hypertrophy outcome because four patients in PVE group were not counted as authors didn't specify the reason for resection ineligibility. The results trend would change if they had been ineligible due to disease progression.

Explanations:

[a] *Lack of allocation concealment and blinding*

[b] *Difference in p-values*

[c] *Not the same trend in studies*

[d] *Few studies and/or small sample size*

[e] *Includes two case series with only twelve patients each*

[g] *RoB assessment: moderate for all comparative studies*

[h] *RoB assessment: low for both case series*

Nomenclature for GRADE table:

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

Inconsistency: NA: Not applicable (only one trial); 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	Patients undergoing major hepatectomy who require preoperative hepatic hypertrophy for resection to be considered viable or who did not achieve adequate hepatic hypertrophy following PVE. All the included studies performed resection on the right side of the liver. The inclusion criteria seem to be in accordance with the intended patient population for the procedure: mainly males (69.1%) with a median age above 60 years, affected mainly by colorectal liver metastases (50.9%). However, patients with diseased liver (such as cirrhosis, fibrosis or NASH) were excluded in three of five studies. Patients with prior chemotherapy or liver intervention were excluded in two and three studies, respectively.
Intervention	All the included studies used simultaneous HPVE except one published more than ten years ago in which HPVE was performed in a sequential way with one to two weeks between PVE and HVE. The sequential approach involves a prolonged waiting period, increasing the risk of tumour progression. In the simultaneous procedure, PVE was performed first, followed by HVE. Studies used a variety of nomenclature to describe the simultaneous procedure (LVD, RASPE and bi-embolisation) – all are technical variations of one another.
Comparators	All the included studies used the first-line preoperative procedure PVE. This is the current standard of care for preoperative hepatic hypertrophy in many surgery departments [24].
Outcomes	Four of five included studies wanted to assess the safety and efficacy of HPVE. Only one study mainly focused on FLR- volume and FLR-function changes after embolisation. The crucial clinical effectiveness outcomes, PHLF and ineligibility to undergo the planned resection, were reported by the three comparative studies. (The two case series, only included for safety outcomes, also reported them, but the results were not assessed in this report). Follow-up time after embolisation ranged from 21 to 40 days but was of 90 days post-surgery. Degree of hypertrophy, FLR-V, and FLR/TLV ratio were the three other main outcomes reported. The crucial patient safety outcomes reported by all five studies were: surgical-related AEs, major AEs after embolisation and surgery, postoperative mortality. The follow-up time for the comparative studies was 90 days post-resection. In one of the case series, follow-up time wasn't mentioned, but one patient died 30 days post-surgery. In the other case series, follow-up ranged from 28 days to 20 months. Recovery time between embolisation and surgery was the second main important safety outcome reported. These outcomes and timing reflect the most important benefits and harms over the short term. However, patient-relevant oncological such as overall survival, recurrence and disease progression would need longer follow-up.
Setting	The three comparative studies were conducted in France, where health care systems are comparable and similar to Austria. Embolisation procedures were realised in an inpatient setting. Patients were discharged either the following day or in the five days following embolisation. One of the case series was carried out in the United States, while the other one was conducted in South Korea. No information concerning the hospitalisation setting was available. No applicability issues are expected from the geographical setting of these studies. However, even though all the included studies are observational, they were all conducted in either a public hospital or cancer centre.

Abbreviations: AE – adverse event, FLR – future liver remnant, HPVE – hepatic and portal vein embolisation, HVE – hepatic vein embolisation, LVD – liver venous deprivation, NASH – non-alcoholic steatohepatitis, PHLF – post-hepatectomy liver failure, PVE – portal vein embolisation, RASPE – radiological associating liver partition and portal vein ligation for staged hepatectomy, TLV – total liver volume

List of ongoing randomised controlled trials

Table A-8: List of ongoing randomised controlled trials of hepatic and portal vein embolisation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03841305 HYPER-LIV01	64 patients (estimated enrolment) Liver metastasis Colon cancer (excluded: cirrhosis) FRL volume <30%	HPVE (named LVD here)	PVE	Compare the increase in volume of the FLR at 3 weeks after embolisation	October 2021	University Hospital, Montpellier Federation Francophone de Cancerologie Digestive
NCT04272931 DRAGON 1[A]	125 patients (estimated enrolment) Colorectal Cancer Liver Metastases FLR <30% in normal livers, or <40% in chemotherapy damaged livers	HPVE (named combined PVE/HVE)	None	Ability of each centre to enrol 3 patients in 12 months without mortality due to the intervention. If this goal is achieved centre will be enrolled in DRAGON 2 (an RCT).	May 2022	Maastricht University Koningin Wilhelmina Fonds

Abbreviation: FLR – future liver remnant, HPVE – hepatic and portal vein embolisation, HVE – hepatic vein embolisation, LVD – liver venous deprivation, PVE – portal vein embolisation, RCT – randomised controlled trial

Notes: A = DRAGON 1 – Training, Accreditation, Implementation and Safety Evaluation of Combined PVE/HVE (DRAGON). PVE/HVE is a novel procedure and requires a safety and feasibility evaluation in a pretrial (DRAGON1) to then be compared in a randomised controlled trial (RCT) to PVE (DRAGON 2: expected to start in 2021, not registered yet in clinical trial websites).

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?
A0006	What are the consequences of the disease or health condition for society?
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?
D0003	What is the effect of the technology on mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) 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)?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Literature search strategies

Search strategy for Cochrane

Search Name: Hepatic & portal vein embolisation	
Last saved: 08/12/2021 20:14:16	
Comment: AUS/LG	
ID	Search
#1	MeSH descriptor: [Hepatectomy] explode all trees
#2	(hepatectom*) (Word variations have been searched)
#3	((excis* OR resect* OR remov*) NEAR liver) (Word variations have been searched)
#4	((liver OR hepatic) NEAR hypertroph*) (Word variations have been searched)
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)
#6	MeSH descriptor: [Embolization, Therapeutic] explode all trees
#7	(emboli*) (Word variations have been searched)
#8	#6 OR #7
#9	MeSH descriptor: [Portal Vein] explode all trees
#10	MeSH descriptor: [Hepatic Veins] explode all trees
#11	((hepatic OR portal OR liver) NEAR vein*) (Word variations have been searched)
#12	#9 OR #10 #11 (Word variations have been searched)
#13	#8 AND #12 (Word variations have been searched)
#14	(PVE):ti,ab,kw (Word variations have been searched)
#15	(HVE):ti,ab,kw (Word variations have been searched)
#16	("portal vein embolisation*")
#17	("hepatic vein* embolisation*")
#18	#13 OR #14 OR #15 OR #16 OR #17
#19	#5 AND #18 (Word variations have been searched)
#20	(conference abstract):pt (Word variations have been searched)
#21	(abstract):so (Word variations have been searched)
#22	(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)
#23	#20 OR #21 OR #22
#24	#19 NOT #23
Total: 38 Hits	

Search strategy for Embase

Search Name: Hepatic & portal vein embolisation		
Comment: AUS/LG		
Search date: 09.12.2021		
No.	Query Results	Results
#64	#62 NOT #63	488
#63	#62 AND 'Conference Abstract'/it	282
#62	(#56 OR #57 OR #60) AND [english]/lim	770
#61	#56 OR #57 OR #60	793
#60	#57 OR #59	226
#59	#18 AND #58	223

#58	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes* NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database* OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	1,398,354
#57	#18 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	94
#56	#19 OR #55	593
#55	#18 AND #54	576
#54	#39 NOT #53	5,002,521
#53	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	3,854,746
#52	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,383,064
#51	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de	1,135,559
#50	(databases NEAR/5 searched):ab	50,151
#49	'update review':ab	119
#48	'we searched':ab AND (review:ti,tt OR review:it)	39,107
#47	review:ab AND review:it NOT trial:ti,tt	930,188
#46	('random cluster' NEAR/4 sampl*):ti,ab,tt	1,508
#45	'random field*':ti,ab,tt	2,570
#44	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt	17,424
#43	'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)	192,359
#42	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)	19,125
#41	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)	310,716
#40	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)	2,771
#39	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	5,637,268
#38	trial:ti,tt	350,881
#37	'human experiment'/de	563,406
#36	volunteer:ti,ab,tt OR volunteers:ti,ab,tt	264,457
#35	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt	401,956
#34	assigned:ti,ab,tt OR allocated:ti,ab,tt	433,115
#33	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt	405,861
#32	crossover:ti,ab,tt OR 'cross over':ti,ab,tt	114,010
#31	(parallel NEXT/1 group*):ti,ab,tt	28,503
#30	'double blind procedure'/de	190,773
#29	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt	252,897
#28	(open NEXT/1 label):ti,ab,tt	92,550
#27	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,405,175

#26	compare:ti,tt OR compared:ti,tt OR comparison:ti,tt	575,001
#25	placebo:ti,ab,tt	333,943
#24	'intermethod comparison'/de	279,752
#23	'randomization'/de	92,347
#22	random*:ti,ab,tt	1,729,344
#21	'controlled clinical trial'/de	435,718
#20	'randomized controlled trial'/de	688,031
#19	#5 AND #17 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	86
#18	#5 AND #17	3,092
#17	#13 OR #14 OR #15 OR #16	9,384
#16	hve:ti,ab	288
#15	pve:ti,ab	2,648
#14	'portal vein embolization'/exp	310
#13	#8 AND #12	7,494
#12	#9 OR #10 OR #11	80,878
#11	(hepatic OR portal OR liver) NEAR/1 vein*	80,878
#10	'hepatic portal vein'/exp	34,790
#9	'liver vein'/exp	10,614
#8	#6 OR #7	124,357
#7	emboli*ation* OR emboli*ing	107,714
#6	'artificial embolization'/exp	103,035
#5	#1 OR #2 OR #3 OR #4	83,783
#4	(liver OR hepatic) NEAR/1 hypertroph*	1,967
#3	(excis* OR resect* OR remov*) NEAR/5 liver	70,130
#2	hepatectom*	37,136
#1	'liver resection'/exp	64,395

488 Hits

Search strategy for Ovid MEDLINE

Database: Hepatic & portal vein embolisation	
Search date: 09.12.2021	
ID	Search
#1	exp Hepatectomy/
#2	hepatectom*.mp.
#3	((excis* or resect* or remov*) adj5 liver).mp.
#4	((liver or hepatic) adj2 hypertroph*).mp.
#5	1 or 2 or 3 or 4
#6	exp Embolization, Therapeutic/
#7	emboli#ation*.mp.
#8	emboli#ing.mp. (
#9	6 or 7 or 8
#10	exp Portal Vein/
#11	exp Hepatic Veins/
#12	((hepatic or portal or liver) adj2 vein*).mp.
#13	10 or 11 or 12
#14	9 and 13
#15	PVE.ti,ab.

#16	HVE.ti,ab.
#17	14 or 15 or 16
#18	5 and 17
#19	limit 18 to (meta analysis or "systematic review")
#20	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.
#21	18 and 20
#22	19 or 21
#23	limit 18 to clinical trial, all
#24	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)
#25	18 and 24
#26	23 or 25
#27	exp epidemiologic studies/ or exp clinical trial/ or comparative study/
#28	((control and study) or program).mp.
#29	27 or 28
#30	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
#31	history.fs. or case report.mp.
#32	30 or 31
#33	29 not 32
#34	18 and 33
#35	22 or 26 or 34
#36	limit 35 to english language
#37	remove duplicates from 36
Total: 515 Hits	

Search strategy for INAHTA

Search Name: Hepatic & portal vein embolisation	
Comment: AUS/LG	
ID	Search
#10	((("Hepatic Veins"[mhe]) OR ("Portal Vein"[mhe])) AND ((emboli*) OR ("Embolization Therapeutic"[mhe]))) OR (Hepatic Vein Embolization*) OR (Portal Vein Embolization*),"2","2021-12-08T22:29:43.000000Z
#9	(("Hepatic Veins"[mhe]) OR ("Portal Vein"[mhe])) AND ((emboli*) OR ("Embolization Therapeutic"[mhe])),"1","2021-12-08T22:29:23.000000Z"
#8	("Hepatic Veins"[mhe]) OR ("Portal Vein"[mhe]),"4","2021-12-08T22:29:04.000000Z"
#7	"Hepatic Veins"[mhe],"0","2021-12-08T22:28:44.000000Z"
#6	"Portal Vein"[mhe],"4","2021-12-08T22:27:44.000000Z"
#5	(emboli*) OR ("Embolization Therapeutic"[mhe]),"196","2021-12-08T22:27:01.000000Z"
#4	emboli*,"175","2021-12-08T22:26:26.000000Z"
#3	"Embolization Therapeutic"[mhe],"62","2021-12-08T22:26:06.000000Z"
#2	Hepatic Vein Embolization*,"2","2021-12-08T22:25:29.000000Z"
#1	Portal Vein Embolization*,"2","2021-12-08T22:25:17.000000Z"
Total: 2 Hits	

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH