NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver

Cancer can start in the liver (primary) or spread to it from another part of the body (metastases). The chemotherapy drug (melphalan) used to treat it can cause side effects in other parts of the body. In this procedure, the blood flow from the liver to the rest of the body is diverted (hepatic vein isolation) while the drug is delivered directly into the liver (percutaneous hepatic artery perfusion). Blood leaving the liver is taken out of the body and filtered to remove the drug, then returned. The aim is to destroy the cancer with a very high dose of the drug (chemosaturation) without causing side effects in the rest of the body.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in June 2019 and updated in August 2020.

Procedure name

- Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver

Professional societies

- British Society of Interventional Radiology
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Association of Surgical Oncology
- Royal College of Radiologists – Faculty of Clinical Oncology
- British Society of Gastroenterology
- British Association for the Study of the Liver

Description of the procedure

Indications and current treatment

The most common types of primary liver cancer are hepatocellular carcinoma (also known as hepatoma) and cholangiocarcinoma. However, cancer in the liver often metastases from other sites such as the lung, colon, stomach and eye (particularly ocular melanoma).

Treatment for primary or metastatic cancer in the liver depends on the location and stage of the cancer and how much liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation (CE), isolated hepatic perfusion and selective internal radiation therapy. In patients with primary liver cancer, surgical removal with curative intent and liver transplantation may be possible. For most patients with liver metastases, treatment with curative intent is not possible.

Regional hepatic arterial delivery of high-dose chemotherapy with isolated hepatic perfusion used to be done using open surgical techniques, which carried a risk of significant morbidity and mortality. It is now done percutaneously: this means that the procedure is less invasive, and it can also be repeated.

What the procedure involves

The aim of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation is to treat liver cancer by delivering a high dose of melphalan chemotherapy directly into the hepatic artery. Blood leaving the liver is diverted out of the body through a catheter and filtered to reduce the level of melphalan before being returned to the circulation. This allows high doses of melphalan chemotherapy to be used, which would otherwise not be tolerated because of severe systemic side effects.

The procedure is done under general anaesthesia. An infusion catheter is inserted into the femoral artery and guided into the hepatic artery. The femoral vein is cannulated and a multi-lumen, double-balloon catheter is inserted into the inferior vena cava and across the hepatic veins. The balloons are inflated and positioned so that all the blood leaving the liver (via the hepatic veins) enters this catheter, rather than the systemic circulation. High doses of melphalan are infused directly into the liver via the hepatic artery infusion catheter over about 30 minutes. Blood leaving the liver passes through an extracorporeal filtration system to remove most of the melphalan and is returned to the circulation via a catheter in the internal jugular vein. Full anticoagulation with heparin is needed throughout the procedure.

The procedure causes significant changes in the patient's haemodynamic status, which must be managed by the anaesthetic team with support from a clinical perfusion scientist.

To reduce the risk of the chemotherapy reaching other organs, some specialists advocate that an angiogram is done first. This is to check the arterial circulation and embolise any branches near the liver supplying other structures, such as the stomach, to prevent the chemotherapy reaching these organs and causing damage.

Outcome measures

The Response Evaluation Criteria in Solid Tumours (RECIST) is used for measuring tumour response using X-ray, CT and MRI. There are 4 categories:

- Complete response: disappearance of all target lesions.
- Partial response: 30% decrease in the sum of the longest diameter of target lesions.
- Progressive disease: 20% increase in the sum of the longest diameter of target lesions.
- Stable disease: small changes that do not meet the above criteria.

Efficacy summary

Tumour response

In a randomised controlled trial (RCT) of 93 patients who had percutaneous hepatic perfusion (PHP) with melphalan or best alternative care for ocular or cutaneous melanoma with liver metastases, the patients treated by PHP had a statistically significantly higher hepatic objective partial response (36%) compared with patients who had best alternative care (2%, $p<0.001$). The objective response rate (by investigator assessment) was also statistically significantly higher in patients treated by PHP (27%) compared with best alternative care (4%, $p=0.003$). Stable disease rate after treatment by PHP was 52% and was 40% for best alternative care.[1]

In a case series of 51 patients who had PHP with melphalan for hepatic metastases of uveal melanoma, there was an overall hepatic response rate of 49% (25/51). This included 3 patients with a complete response (6%) and 22 patients with a partial response (43%). The proportion of patients with stable disease for more than 3 months was 33% and, for more than 6 months, was 22%.[2]

In a case series of 60 patients with hepatic metastases of ocular melanoma (n=30), cholangiocarcinoma (n=14), hepatocellular carcinoma (n=6) or other secondary liver malignancies (n=10), the overall response rate was 33% (18/54) and the overall disease stabilisation rate was 70% (38/54). The overall response rate in patients with hepatic metastases of ocular melanoma alone was 42% (11/26).[3]

In a case series of 18 patients with unresectable isolated hepatic metastases from uveal melanoma who had PHP with melphalan, in the first cycle (18 patients), 44% of patients had a partial response, 39% of patients had stable disease and 17% had progressive disease. In the second cycle (9 patients), the proportion of patients who had a partial response was 89%. The study reported that 11% of patients had progressive disease. In the third cycle (6 patients), 83% of patients had a partial response and 17% had stable disease. In the fourth cycle of treatment (2 patients), both patients had progressive disease.[5]

In a case series of 16 patients who had PHP with melphalan treatment for liver-dominant metastatic uveal melanoma, in the first cycle of treatment (15 patients) had a 60% partial response rate, 33% of patients had stable disease and 7% of had progressive disease. In the second cycle (6 patients), 67% of patients had a partial response and 33% had stable disease. In the third cycle (3 patients), all patients had stable disease. One patient, who had 3 more treatments, had stable disease in the fourth and fifth treatment cycle. Their disease progressed in the sixth cycle.[6]

In a case series of 15 patients who had PHP with melphalan for unresectable intrahepatic cholangiocarcinoma, in the first cycle, 1 patient had a complete response, 2 patients (13%) had a partial response, 8 patients (53%) had stable disease and 3 patients (20%) had progressive disease. In the second cycle (5 patients), 1 patient had a partial response, 3 patients (60%) had stable disease and 1 patient had progressive disease. The third, fourth, and fifth treatment cycles were done in 2 patients with stable disease during long-term follow up.[7]

In a case series of 35 patients who had PHP with melphalan for unresectable liver metastases from ocular melanoma, the overall response rate was 72% (23/32) with a complete response in 3% (1/32) of patients and a partial response in 69% (22/32) of patients. In the same study, the confirmed hepatic response rate was 81% (26/32), with a complete response in 3% (1/32) of patients and a partial response in 78% (25/32) of patients.[9]

In a case series of 14 patients with unresectable hepatic metastases from solid tumours who had PHP with melphalan treatment, of 12 patients who had PHP treatments, 1 patient had a complete response, 6 patients (50%) had a partial response and 5 patients (42%) had stable disease.[10]

In a case series of 19 patients with unresectable hepatic metastases from ocular melanoma who had PHP with melphalan, 53% (10/19) had a partial response and 47% (9/19) had stable disease. [11]

Overall survival

In the RCT of 93 patients, median overall survival for patients having PHP was 10.6 months (95% confidence interval [CI] 6.9 to 13.6). For best alternative care, overall survival was 10.0 months (95% CI 6.0 to 13.1), which was not statistically significant. But, the comparison was not appropriate, because 57% of patients having best alternative care had crossover treatment of PHP with melphalan.[1]

In the case series of 51 patients, median overall survival was 15.3 months.[2]

In the case series of 60 patients, median overall survival from the first diagnosis of the metastatic disease was 56 months and, from the first treatment, was 9 months.[3]

In a non-randomised comparative study of 30 patients who had radioembolisation (Y90), PHP or hepatic CE for liver metastases from cutaneous or uveal melanoma, the median overall survival was the longest, but not statistically significant, for PHP at 608 days, compared with 295 days for Y90 and 265 days for hepatic CE (p=0.24). In the multivariate analysis, the overall survival was statistically significantly better for patients treated by PHP compared with Y90 (hazard ratio [HR] 0.12, 95% CI 0.02 to 0.78, p=0.03). But, the overall survival was not statistically significantly different between patients treated by PHP compared with CE (HR 0.47, 95% CI 0.17 to 1.25, p=0.13).[4]

In the case series of 18 patients, median overall survival was 9.6 months (range 1.6 to 41.0) and 1-year survival rate was 44%.[5]

In the case series of 16 patients, median overall survival for treatment with PHP was 27.4 months (95% CI 4.1 to 35.4) and 1-year survival rate was 58%.[6]

In the case series of 15 patients, median overall survival from initial diagnosis was 26.9 months and median overall survival from the first PHP treatment was 7.6 months. The 1-year survival rate was 40%. The subgroup analysis showed that the median overall survival from the first PHP treatment for patients with liver-only metastases was 12.9 months and for patients with locoregional lymph node involvement was 4.8 months (p<0.01).[7]

In the case series of 35 patients, 17% (6/35) of patients were still alive after a median follow-up of 19 months. The 1- and 2-year overall survival rates were 77% and 43% respectively. Median overall survival was 19.1 months for all included patients (n=35). It was statistically significantly longer in patients whose disease responded than in patients whose disease did not respond (27.5 months compared with 11.9 months p<0.001). [9]

In the case series of 19 patients, median overall survival was 26.4 months after initial diagnosis and 16.7 months after the first PHP with melphalan treatment. The estimated overall survival rates were 21% (95% CI 4% to 100%) from first imaging to 5 years, 79% (95% CI 61% to 100%) at 1 year after chemosaturation and 60% (95% CI 38% to 96%) at 2 years after chemosaturation. [11]

Progression-free survival

In the RCT of 93 patients, median hepatic progression-free survival for patients who had PHP was 7.0 months (95% CI 5.2 to 9.7). This was statistically significantly longer than the hepatic progression-free survival of those having best alternative care, which was 1.6 months (95% CI 1.5 to 2.9; p<0.0001). There was also a statistically significant improvement in overall progression-free survival for patients having PHP with melphalan (5.4 months, 95% CI 3.4 to 8.1) compared with patients having best alternative care (1.6 months, 95% CI 1.5 to 2.3; p=0.0001).[1]

In the case series of 51 patients, overall hepatic progression-free survival was 9.1 months and overall progression-free survival was 8.1 months.[2]

In the case series of 60 patients, median hepatic progression-free survival was 5 months and median progression-free survival was 4 months.[3]

In the non-randomised comparative study of 30 patients, median hepatic progression-free survival was statistically significantly longer for PHP (361 days) than for Y90 (54 days) or CE (80 days, p=0.001). Median progression-free survival was also statistically significantly longer (245 days) for patients who had PHP compared with the other 2 treatments (progression-free survival for Y90 was 54 days and progression-free survival for CE was 52 days, p=0.03). In the multivariate analysis, hepatic progression-free survival was statistically significantly longer in patients who had PHP compared with patients who had Y90 (HR 0.11, 95% CI 0.03 to 0.49, p=0.004). Hepatic progression-free survival was also statistically significantly longer in patients who had PHP compared with patients who had CE (HR 0.31, 95% CI 0.12 to 0.81, p=0.02). Similarly, progression-free survival was statistically significantly better for patients who had PHP compared with patients who had Y90 (HR 0.17; 95% CI 0.04 to 0.63, p=0.008). Progression-free survival was also statistically significantly better for patients who had PHP compared with patients who had CE (HR 0.37; 95% CI 0.14 to 0.94; p=0.04).[4]

In the case series of 18 patients, median progression-free survival was 12.4 months (range 0.9 to 41.0 months).[5]

In the case series of 16 patients, progression-free survival was 11.1 months (95% CI 4.9 to 23.6) after the first cycle of treatment and 9.6 months (95% CI, 7.0 to 19.76) after the second cycle.[6]

In the case series of 15 patients, median hepatic progression-free survival was 131 days and a median progression-free survival was 122 days.[7]

In the case series of 35 patients, median progression-free survival was 7.6 months (95% CI 4.9 to 10.3) and median hepatic progression-free survival was 11.2 months (95% CI 9.0 to 13.4). The 1-year progression-free survival rate was 27%. [9]

In the case series of 19 patients, progression-free survival was 751.8 days ± 515.5 years since first imaging and 427.8 ± 295.2 days since the first PHP with melphalan treatment. [11]

Quality of life

In the case series of 35 patients, the global health status scores (from 0 [low level of functioning] to 100 [high level of functioning], evaluated with the EORTC QLQ-C30 v3.0 form) did not statistically significantly change after treatment. Before treatment the median was 83 (range 33 to 100) compared with 83 (range 25 to 100) 6 months after the first PHP with melphalan treatment. Only physical functioning was statistically significantly worse 6 weeks after the second PHP with melphalan treatment (p=0.011). It returned to pre-treatment level 3 months later.[9]

Safety summary

Death

Adverse events that caused death were reported in 4% (4/93) of patients in the RCT of 93 patients. 2 deaths happened because of bone marrow suppression (1 from complication of neutropenia and 1 from streptococcal sepsis). 1 patient died because of progressive hepatic failure and 1 patient from the crossover population died because of gastric perforation.[1]

One patient died at 46 days after having the first cycle of PHP treatment in the case series of 15 patients. The cause of death was sepsis and liver failure.[7]

One patient died in the case series of 14 patients. The patient died 30 hours after chemosaturation with PHP, after developing a giant retroperitoneal haematoma.[10]

Haematological toxicity

In the RCT of 93 patients, grade 3 or 4 anaemia was reported in 60% (42/70) of patients during the periprocedural period and 63% (44/70) of patients during the postprocedural period. Thrombocytopenia of grade 3 or 4 was reported in 74% (52/70) of patients in the periprocedural period and 80% (56/70) of patients in the postprocedural period. Neutropenia (grade 3 or 4) was reported in 4% (3/70) of patients during the periprocedural period and 86% (60/70) of patients in the postprocedural period. Increased international normalised ratio (INR) happened in 20% (14/70) of patients but only 1 patient had an increased INR during the postprocedural period. Prolonged activated partial thromboplastin time was reported in 26% (18/70) of patients during the periprocedural period.[1]

In the case series of 51 patients, grade 3 or 4 anaemia was reported in 29% (15/51) of patients, grade 3 or 4 thrombocytopenia was reported in 31% (16/51) and grade 3 or 4 neutropenia was reported in 31% (16/51).[2]

Grade 3 or 4 anaemia was reported in 45% (27/60) of patients in the case series of 60 patients. The study also reported grade 3 or 4 thrombocytopenia in 80% (48/60) of patients and grade 3 or 4 leukopenia in 32% (19/60) of patients.[3]

In the case series of 18 patients, anaemia was reported in 3% (1/35), leukopenia in 31% (11/35) of procedures and thrombocytopenia in 23% (8/35) of procedures.[5]

In the case series of 16 patients, who had 28 procedures in total, anaemia was reported in 96% (27/28) of the procedures done. Similarly, leukopenia was reported in 96% (27/28) and thrombocytopenia was reported in 75% (21/28) of the total procedures done.[6]

In the case series of 15 patients who had 26 procedures in total, anaemia that needed a transfusion was reported in 27% (7/26) of the total procedures done. Thrombocytopenia that needed a platelet transfusion was reported in 23% (6/26) of procedures done. Leukopenia that needed treatment with a granulocyte-colony stimulating factor was reported in 15% (4/26) of the total procedures done.[7]

In a case series of 35 patients who had PHP with melphalan for unresectable liver metastases from ocular melanoma, anaemia was reported in 18% (6/33) of patients. Thrombocytopenia was reported in 55% (18/33) of patients, leukopenia was reported in 75% (25/33), neutropenia was reported in 67% (22/33) and lymphocytopenia was reported in 85% (28/33). All of these were classified as grade 3 or 4.[8]

In the case series of 14 patients, who had a total of 18 PHP treatments, anaemia was reported in 72% (13/18) of procedures. Thrombocytopenia was reported in 56% (10/18) and leukocytopenia was reported in 56% (10/18).[10]

Platelet count decreased from a mean of 251.7/nL (SD 65.8) before the first PHP with melphalan procedure to a mean of 104.2/nL (SD 45.4) following the procedure in a case series of 19 patients with unresectable hepatic metastases from ocular melanoma who had PHP with melphalan. [11]

Liver toxicity

In the RCT of 93 patients, 20% (14/70) of patients had increased aspartate transaminase (AST) enzyme, 10% (7/70) had increased bilirubin and 37% (26/70) had decreased albumin during the periprocedural period. During the postprocedural period, the proportion of patients who had an increased AST rate was 10% (7/70), those who had increased bilirubin was 14% (10/70) and those with decreased albumin was 6% (4/70).[1]

In the case series of 51 patients, transaminitis was reported in 29% (15/51) of patients, and was classified as grade 3 or 4 in 6% (3/51).[2]

In the case series of 60 patients, increased AST enzyme (grade 3 or 4) was reported in 48% (29/60) of patients. An increased level of alanine aminotransferase (grade 3 or 4) was reported in 27% (16/60) of patients and increased serum bilirubin was reported in 15% (9/60) of patients.[3]

In the case series of 16 patients who had 28 procedures in total, liver toxicity was reported in 46% (13/28) of the total procedures done.[6]

Transaminitis was reported in 11% (2/18) of the total procedures done in the case series of 14 patients.[10]

Cardiovascular events

Cardiac toxicity was reported in 17% (12/70) of patients during the periprocedural period in the RCT of 93 patients. This included raised troponin in 6 patients and sinus tachycardia in 2 patients. 1 patient had myocardial infarction, 1 had atrial fibrillation, 1 had pericardial effusion and 1 had ventricular tachycardia. Hepatic artery spasm was reported in 67% of patients. Cerebral ischaemia was reported in 1 patient and facial paresis was reported in 1 patient.[1]

Cardiac ischaemia was reported in 10% (5/51) of patients in the case series of 51 patients. Arrythmias of any grade were also reported in 10% (5/51), which

included 3 cases of ventricular tachycardia and 1 supraventricular tachycardia. A cerebrovascular event was reported in 4% (2/51) of patients in the study.[2]

Cardiovascular complications reported in the case series of 60 patients were atrioventricular block (1 patient) and ischaemic insults in 2 patients.[3]

In the case series of 18 patients, periprocedural hypotension was reported in 6% (2/35) of procedures, and tachycardia, coagulopathy and ventricular fibrillation were each reported during 1 procedure. Asystole, aneurysma spurium, and hypertensive crisis were each reported once up to 30 days after the procedure.[5]

In the case series of 16 patients who had 28 procedures in total, cardiovascular events occurred in 1 patient.[6]

Hypotension and tachycardia were reported during the periprocedural period in the case series of 15 patients (values not reported). Temporary stroke was reported in 1 patient in the study.[7]

Coronary ischaemia was reported in 5% (2/43) of procedures in the case series of 19 patients. [11]

Febrile neutropenia and infection

Febrile neutropenia was reported in 17% (12/70) of patients in the RCT of 93 patients. Streptococcal sepsis was reported in 1 patient in the study, who died because of the infection (described previously).[1]

Infection was reported in 6% (2/35) of procedures in the case series of 18 patients.[5]

Infection or inflammation was reported in 18% (5/28) of the total procedures done in the case series of 16 patients.[6]

In the case series of 35 patients, 2 patients had febrile neutropenia, 1 had febrile neutropenia with mucositis or oesophagitis, 1 had prostatitis, 1 had sepsis with bacterial pharyngitis and retropharyngeal abscess, 1 had a bladder infection, 1 had cystitis, 1 had an upper respiratory tract infection and 1 had a vulva infection.[8]

Pneumonia was reported in 4 patients and otitis was reported in 1 patient in the case series of 15 patients. The pneumonias were treated with antibiotics. [7]

Febrile neutropenia was reported in 2 patients in the case series of 14 patients.[10]

Haemorrhage

Haemorrhagic events were reported in 20% (10/51) of patients in the case series of 51 patients, 2 cases of which were classified as grade 3 or 4. Haemorrhagic events included 1 patient with disseminated intravascular coagulation, 1 patient with intraabdominal bleeding and 1 patient with intracerebral haemorrhage.[2]

Ulcerous bleeding was reported in 3% (2/60) of patients in the case series of 60 patients.[3]

Haematemesis and epistaxis were reported in 1 procedure each in the case series of 18 patients.[5]

Bleeding was reported in 1 patient in the case series of 15 patients.[7]

In the case series of 35 patients, post-procedural haemorrhage was reported in 31% (11/35) of patients including vaginal haemorrhage with grade 2 anaemia in 1 patient.[8]

Vaginal bleeding was reported in 1 patient in the case series of 14 patients. This was probably induced by heparin. The patient did not receive chemosaturation with PHP and recovered without sequelae. Retroperitoneal haematoma was reported in 1 patient in the study, who died 30 hours after the treatment (described previously).[10]

Transfemoral bleeding was reported in 1 patient in the case series of 19 patients; it was treated with surgery. [11]

Thromboembolic events

In the case series of 51 patients, 14% (7/51) of patients had thromboembolic events during the study period. These included pulmonary embolism (2 patients), lower limb deep vein thrombosis (2 patients), and thrombus in inferior vena cava (1 patient), left internal jugular vein (1 patient) and vascular access site (1 patient).[2]

Inferior vena cava thrombosis and liver vein thrombosis were reported in 1 procedure each in the case series of 18 patients.[5]

Pulmonary embolism was reported in 2 patients in the case series of 35 patients.[8]

Other adverse events

Decreased serum calcium was reported in 23% (16/93) of patients in the RCT of 93 patients, all of which happened in the periprocedural period. End organ

toxicity that was caused by the procedure-related hypotension was also reported in the study (no values reported).[1]

Pulmonary oedema was reported in 6% (3/51) of patients in the case series of 51 patients.[2]

Oedema, ascites or pleural effusion caused by overhydration or hypoalbuminaemia were reported in 22% (13/60) of patients in the case series of 60 patients. Puncture site complications were reported in 3% (2/60) of patients, dissection of the common hepatic artery in 1 patient and femoral pseudoaneurysm in 1 patient.[3]

The non-randomised comparative study of 30 patients reported complications of PHP treatment in 60% (6/10) of patients (no details provided). [4]

In the case series of 18 patients, 1 balloon rupture was reported during the periprocedural period. In the postprocedural period, oedema was reported after 2 procedures. Ascites, hypoxia, right leg compartment syndrome, pleural effusion and vertigo were all reported after 1 procedure each. [5]

Nephrotoxicity was reported in 7% (2/28) of total procedures done in the case series of 16 patients. [6] Acute renal failure, ascites, oedema and pseudoaneurysm were each reported in 1 patient in the case series of 15 patients.[7]

Generalised oedema or pleural effusion, or both, were reported in 23% (8/35) of patients in the case series of 35 patients.[8]

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver. The following databases were searched, covering the period from their start to 10 August 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with primary or metastatic cancer in the liver.
Intervention/test	Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 351 patients from 1 RCT, 1 non-randomised comparative study and 9 case series[1-11].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver

Study 1 Hughes M (2016)

Details

Study type	**Randomised Controlled Trial**
Country	USA
Recruitment period	2006 - 2009
Study population and number	**n= 93** (44 PHP-Mel vs 49 BAC) Patients with ocular or cutaneous melanoma with liver metastases
Age and sex	Percutaneous hepatic perfusion with melphalan (PHP -Mel): Median 55 years; = 52% (23/44) male Best alternative care (BAC): Median 56 years; 45% (22/49) male
Patient selection criteria	Inclusion criteria: patients with biopsy proven, unresectable melanoma metastatic to the liver; Eastern Cooperative Oncology Group performance status of <2, a serum bilirubin <2.0 mg/dl, a platelet count >100,000, serum creatinine\1.5 mg/dl, and liver function tests <10 times the upper limit of normal. Exclusion criteria: brain metastases, conditions precluding anticoagulation, latex allergy, cirrhosis, or significant portal hypertension, patients with surgically resectable disease.
Technique	The PHP-Mel procedure was done under general anaesthesia with percutaneous technique that allows delivery of high dose melphalan directly to the liver via the hepatic artery over 30 min. A unique double-balloon inferior vena cava catheter system (Delcath Systems) was used. Melphalan was administered at a dose of 3 mg/kg based on ideal body weight. The melphalan dose on subsequent PHPs was reduced to 2.5 mg/kg if a dose-limiting toxicity (DLT) was encountered. Primary BAC treatment strategies included systemic chemotherapy with dacarbazine/temozolomide (42.9 %), carboplatin/taxol (6.1 %), chemoembolisation (22.4 %), radioembolisation (6.1 %), or supportive care (18.4 %).
Follow up	**Mean follow up – not reported**
Conflict of interest/source of funding	The study was funded by the Intramural Program of the National Cancer Institute, National Institutes of Health. Additional funding was supplied via a Cooperative Research and Development Agreement (CRADA) between Delcath Systems, Inc., and the Surgery Branch of the National Cancer Institute. No conflict of interest was reported.

Analysis

Follow-up issues: While on active treatment, patients were followed and imaged at 6 weeks intervals. When off active treatment, the follow up was arranged disease progression at every 8 weeks for the first year, every 3 months for the second year, every 4 months in third year every 6 months in the fourth year and yearly thereafter. Survival was assessed 6 monthly for 2 years and yearly thereafter.

Study design issues: A phase 3 randomised, multicentre clinical trial comparing percutaneous hepatic perfusion (PHP) with best available care (BAC). Patients were initially recruited through the National Cancer Institute and expanded to multiple centres (total 9 institutions across US). Forty-four patients were randomly assigned to receive PHP-Mel (47.3 %) and 49 (52.7 %) assigned to receive best alternative care (BAC). Primary endpoint was hepatic progression-free survival (hPFS). Secondary endpoints included hPFS, xPFS (defined as the time from the date of randomisation to the first

observation of extrahepatic disease progression or death due to any cause), hepatic objective response (hOR), objective response rate (ORR), overall PFS (oPFS), overall survival (OS), and safety.

All treatment decisions were based on investigator (INV) assessment of response. Survival and response calculations were based on a blinded, outside independent image review (IRC). 46 patients per treatment arm had 80 % power to detect a median difference of 4 months between treatment groups for the primary endpoint. Data from intention to treat (ITT) only were presented.

Study population issues: Patient and tumour clinicopathologic characteristics were similar between the 2 groups. All patients had extensive liver disease, 51 % of patients having 5 or more liver lesions at baseline and a mean hepatic replacement with tumour of 31.6 %. On progression of disease, crossover to PHP-Mel treatment occurred in 28 of 49 patients (57.1 %) at a mean time from randomisation of 3.8 months (range 1.1– 23.7); however, only 25 of the 28 crossover patients received PHP-Mel. Of the 70 patients who had PHP-Mel treatment (including crossover patients), 24 (34.3 %) discontinued treatment due to adverse events.

Other issues:

Key efficacy and safety findings

Efficacy

Number of patients analysed: **93** (44 PHP- Mel vs 49 BAC)

Objective Response

Response	PHP-Mel (n)	BAC	P
Hepatic Objective response (partial)	36.4% (16)	2.0% (1)	<0.001
Stable disease rate	52.3% (23)	40.8 % (20)	NR
Objective Response Rate* (partial)	27.3%	4.1%	0.003

*By investigator assessment

Median Hepatic Progression-Free Survival (hPFS)

- PHP-Mel = 7.0 months (95% CI, 5.2-9.7)
- BAC= 1.6 months (95% CI, 1.5-2.9), p<0.0001

Median Overall Progression-Free Survival (oPFS)

- PHP-Mel= 5.4 months (95% CI, 3.4-8.1)
- BAC = 1.6 months (95% CI, 1.5-2.3), p=0.0001

Median Overall Survival

- PHP-Mel= 10.6 months (95% CI 6.9-13.6)
- BAC = 10.0 months (95% CI 6.0-13.1), *p*= NS

(57.1 % of BAC arm had crossover treatment of PHP-Mel)

Safety

Deaths

4 deaths (4.3%) from 70 patients with PHP-Mel treatment:

- 2 were associated with bone marrow suppression (1 each from complication of neutropenia and streptococcal sepsis),
- 1 death from progressive hepatic failure.
- 1 death occurred in the crossover population, resulting from gastric perforation.

Adverse events (Grade 3/4)

AEs	Peri-procedural, (n=70) (%)	Post-procedural (n=70) (%)
Anaemia	42(60.0)	44 (62.9)
Thrombocytopenia	52(74.3)	56(80.0)
Prolonged aPTT	18(25.7)	NA
Increased INR	14(20.)	1(1.4)
Increased AST	14(20.)	7(10.0)
Decreased albumin	26(37.1)	4(5.7)
Increased bilirubin	7(10.0)	10(14.3)
Decreased serum calcium	16(22.9)	NA
Febrile Neutropenia	NA	12(17.1)
Neutropenia	3(4.3)	60(85.7)

Other adverse events:

Peri-procedural

- Procedure associated hypotension – values not reported

	- Hepatic artery spasm – 67% - End organ toxicity (attributable to hypotension) – values not reported - Cardiac toxicity such as raised troponin (n=6), sinus tachycardia (n=2) myocardial infarction (n=1) atrial fibrillation (n=1), pericardial effusion (n=1) and ventricular tachycardia (n=1) - Cerebral ischaemia (n=1) - Facial paresis (n=1) Post-procedural - Venous thrombosis - Acute cholecystitis - Gastroduodenal ulcer **Discontinuation of therapy** - Of the 70 patients who had PHP-Mel treatment (including crossover patients), 24 (34.3%) discontinued treatment due to adverse events, 20 patients (28.6%) due to disease progression, 1 due to patient's own decision and 9 because of investigators opinion.
Abbreviations used: PHP-Mel, percutaneous hepatic perfusion with melphalan; BAC, best available Care; aPTT, partial thromboplastin time; INR, International normalised ratio; AST, aspartate aminotransferase.	

Study 2 Karydis I (2018)

Details

Study type	**Case series**
Country	UK and US (2 institutions)
Recruitment period	2008 - 2016
Study population and number	**n=51** Patients with metastatic uveal melanoma (UM)
Age and sex	Mean 57.9 years; 54.9% (28/51) Female
Patient selection criteria	Inclusion criteria: Patients with histologically confirmed UM who had percutaneous hepatic perfusion with melphalan (M-PHP). Patients with previous systemic or liver-directed treatments other than M-PHP were allowed if the related adverse events ad either resolved or were not expected to impact the safety or efficacy of the procedure. Known or suspected extrahepatic disease were also not excluded if disease was non-progressive.
Technique	PHP treatment was done using Delcath Hepatic Delivery System. The dose of melphalan was calculated at 3 mg/kg, corrected for the patient's ideal body weight (maximum dose: 220 mg). Repeat M-PHP procedures were planned at approximately 8-week intervals.
Follow up	**Median 367 days**
Conflict of interest/source of funding	The study was funded by NIHR Southampton Experimental Medicine Centre. 1 author received honoraria for lecturing and has acted as a medical advisor to Delcath Systems Inc. 2 other authors received a travel grant by Delcath Systems Inc. 1 author served on the medical advisory board for Delcath Systems and has research funding from Delcath Systems. All remaining authors have declared no conflicts of interest.

Analysis

Follow-up issues: Repeated M-PHP was planned at 8 weeks intervals. Radiological assessment took place as clinically indicated, typically 6-8 weeks after each treatment. At data collection cut-off point (median 367 days), 2 patients were lost to follow up,17 were still alive and 32 had passed away.

Study design issues: A retrospective analysis of outcomes data of metastatic uveal melanoma patients receiving M-PHP at 2 institutions in UK and US. Data were collected retrospectively from the electronic medical records. Tumour response and toxicity were evaluated retrospectively using RECIST 1.1 and Common Terminology Criteria for Adverse Events (CTCAE). Either a dedicated liver MRI or triple phase CT was done to assess tumour response. 51 patients completed 134 M-PHP procedures (median 2 M-PHP). Kaplan–Meier method was used for survival analysis; long-rank test used to compare curves and determine the P-values. SPSS was used for Cox regression.

Study population issues: All patients had pathologically confirmed metastatic UM to liver and radiologically confirmed hepatic progression; 8/51 (15.7%) also had limited extrahepatic disease. 27.5% of patients (n=14) had previous liver directed treatments (e.g. resection, ablations, TACE or SIRT) and 29.4% (n=15) had previous systemic treatment such as immunotherapy, chemotherapy or clinical trial.

Patients treated in Southampton received up to 4 treatments, those treated in US centre received up to 6 treatment courses. At median follow up of 12.2 months, a median of 2 cycles of M-PHP per patient were done; 7 patients were still continuing on treatment; 15 had completed planned full-course; 29 patients discontinued early(9 due to treatment related toxicity, 17 due to disease progression and 3 due to patient preference).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 51

Hepatic Response
Complete Hepatic response = 5.9% (3/51)
Partial Hepatic Response = 43.1% (22/51)
Overall Hepatic response (hORR) = 49.0% (25/51)

Stable disease for > 3 months = 33.3% (17/51)
Stable disease for > 6 months = 21.6% (11/51)

Overall Response
Complete Overall response = 3.9% (2/51)
Partial Overall response= 43.1% (22/51)
Overall response rate (ORR) = 47.0 % (24/51)

Survival analysis
Median OS= 15.3 months
Overall PFS = 8.1 months
Overall hPFS = 9.1 months</td><td>Deaths
No treatment related deaths.

Adverse events
<table><tr><th>AE</th><th>Any grade, N (%)</th><th>Grade 3-4, N (%)</th></tr><tr><td>Anaemia</td><td>51 (100.0)</td><td>15 (29.4)</td></tr><tr><td>Neutropenia</td><td>22 (43.1)</td><td>16 (31.3)</td></tr><tr><td>Thrombocytopenia</td><td>50 (98.0)</td><td>16 (31.3)</td></tr><tr><td>Haemorrhagic event</td><td>10 (19.6)</td><td>2(3.9)</td></tr><tr><td>Thromboembolic event</td><td>7(13.7)</td><td>6(11.8)</td></tr><tr><td>Arrhythmias</td><td>5(9.8)</td><td>4 (7.8)</td></tr><tr><td>Pulmonary oedema</td><td>3(5.9)</td><td>3(5.9)</td></tr><tr><td>Cardiac Ischaemia</td><td>5 (9.8)</td><td>5(9.8)</td></tr><tr><td>Cerebrovascular event</td><td>2 (3.9)</td><td>0</td></tr><tr><td>Transaminitis</td><td>15(29.4)</td><td>3 (5.9)</td></tr></table>
Haemorrhagic events include 1 case each of DIC, intra-abdominal bleeding and intracerebral haemorrhages.
Thromboembolic events include 2 pulmonary embolism, 2 lower DVT and 1 each for inferior vena cava, left internal jugular vein and vascular access site related thrombus.
Arrythmias include 3 cases of ventricular tachycardia and 1 supraventricular tachycardia. There were 5 cases of post-op Troponin elevation.

Other reported adverse events were fatigue, mucositis, nausea, vomiting, epigastric pain, rash and constipation.</td></tr>
<tr><td colspan="2">Abbreviations used: OS, overall survival; PFS, progression-free survival; hPFS, hepatic progression-free survival; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis.</td></tr>
</table>

Study 3 Schönfeld L (2020)

Details

Study type	**Retrospective case series**
Country	Germany (single centre)
Recruitment period	2014 to 2019
Study population and number	**n=60** (141 procedures) patients with hepatic metastases of ocular melanoma (n=30), cholangiocarcinoma (n=14), hepatocellular carcinoma (n=6) or other secondary liver malignancies (n=10).
Age and sex	Median age 60.5 years; 40% (24/60) male
Patient selection criteria	Inclusion criteria: adequate haematologic, renal, and hepatic function (haemoglobin > 8 g/dL; leukocyte count > 2 thsd/µL; platelets > 50 thsd/µL, serum creatinine > 60 µmol/L, bilirubin ≤ 3 × upper limit of normal [ULN], maximum Child–Pugh A). Exclusion criteria: history of transient ischaemic attacks, heart failure with a left-ventricular ejection fraction < 40%, or significant chronic obstructive or restrictive pulmonary disorder.
Technique	Chemosaturation with percutaneous hepatic perfusion (CS-PHP; Hepatic CHEMOSAT® Delivery System; Delcath Systems Inc, USA) Patients received single-shot antibiotics peri-interventionally and granulocyte colony-stimulating factor (G-CSF) 24–72 h post-intervention.
Follow up	**Median follow-up 27 months**
Conflict of interest/source of funding	Arndt Vogel has received honoraria from Delcath Systems Inc for Advisory Boards and speaker activities. Frank Wacker reports grants and personal fees from Delcath Systems, Inc during the conduct of the study; grants from Siemens Healthineers, Promedicus Ltd., and personal fees from Novartis Pharma GmbH, outside the submitted work.

Analysis

Follow-up issues: 54 patients (90%) were available for radiological response assessment. One patient with ocular melanoma (OM) died due to sepsis shortly after the first CS-PHP. Two other patients with OM died due to rapid tumour progression. Both patients had a high tumour burden and tumour volume. The remaining 3 patients were lost to follow-up before imaging could be done.

Study design issues:
Overall response rates (ORR) were assessed according to RECIST1.1. Median overall survival (mOS), median progression-free survival (mPFS), and median hepatic PFS (mhPFS) were analysed using the Kaplan-Meier estimation. Toxicity was assessed according to the CTCAEv5.0.

Study population issues:
Seven patients had extra-hepatic tumour manifestations (11.9%) including bone (n=4), pulmonary (n=2), and cutaneous (n=1) metastases. Patients with hepatic metastases of OM had statistically significantly higher levels of lactate dehydrogenase (LDH) (p=0.013).
All patients had had extensive pretreatment with standard therapies, indicating that CS-PHP was done in a salvage setting following the use of standard therapies.

Other issues: Part of this study population (n=29; 54 interventions) had previously been included and described in the Kirstein (2017) study (in the appendix).

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 54

Procedural outcomes
A maximum of 7 procedures were done in 1 patient.
Most patients had at least 2 procedures (n=118; 83.7%).
Median time between first procedure and second procedure was 63 (IQR 45–98) days.
Median time between first procedure and first imaging control was 50 (IQR 38–75) days.
Median time between first diagnosis and first CS-PHP was 25 (IQR 9–61.75) months.
Median time of hospitalisation after the first CS-PHP was 7.5 (IQR 6–11) days

Response assessment
Overall response rate (ORR): 33.3% (18/54)
Overall disease stabilisation rate: 70.3% (38/54)
ORR among ocular melanoma patients: 42.3% (11/26)
ORR among patients with cholangiocarcinoma: 30.8% (4/13)
ORR among patients with other secondary malignancies: 33.3% (3/9)
ORR among patients with hepatocellular carcinoma: 0%

Independent response-associated factors were normal levels of lactate dehydrogenase (odds ratio [OR] 13.7; p=0.015) and diagnosis with OM (OR 9.3; p=0.028).

Survival analysis
Median OS from first diagnosis: 56 months
Median OS from first CS-PHP: 9 months

Median hPFS: 5 months
Median PFS: 4 months

Patients with OM had numerically longer mOS, mPFS, and mhPFS (12, 6, and 6 months, respectively; not statistically significant).</td><td>Adverse events as assessed by CTCAE v4.03 after first and after overall CS-PHP (n=60 patients)
<table><tr><td></td><td colspan="2">After 1st CS-PHP</td><td colspan="2">Overall</td></tr><tr><td></td><td>n</td><td>%</td><td>n</td><td>%</td></tr><tr><td>Platelet concentrate</td><td>12</td><td>20.3</td><td>18</td><td>30.0</td></tr><tr><td>Erythrocyte concentrate</td><td>11</td><td>18.6</td><td>19</td><td>31.7</td></tr><tr><td>Grade 3 thrombopenia</td><td>15</td><td>25.0</td><td>28</td><td>46.7</td></tr><tr><td>Grade 4 thrombopenia</td><td>14</td><td>23.3</td><td>20</td><td>33.3</td></tr><tr><td>Grade 3 anaemia</td><td>19</td><td>31.7</td><td>26</td><td>43.3</td></tr><tr><td>Grade 4 anaemia</td><td>0</td><td>0</td><td>1</td><td>1.7</td></tr><tr><td>Grade 3 leukopenia</td><td>4</td><td>6.7</td><td>8</td><td>13.3</td></tr><tr><td>Grade 4 leukopenia</td><td>7</td><td>11.7</td><td>11</td><td>18.3</td></tr><tr><td>Grade 3 AST increase</td><td>11</td><td>18.3</td><td>20</td><td>33.3</td></tr><tr><td>Grade 4 AST increase</td><td>7</td><td>11.7</td><td>9</td><td>15.0</td></tr><tr><td>Grade 3 ALT increase</td><td>4</td><td>6.7</td><td>12</td><td>20.0</td></tr><tr><td>Grade 4 ALT increase</td><td>2</td><td>3.3</td><td>4</td><td>6.7</td></tr><tr><td>Grade 3 hyperbilirubinaemia</td><td>5</td><td>8.3</td><td>8</td><td>13.6</td></tr><tr><td>Grade 4 hyperbilirubinaemia</td><td>1</td><td>1.7</td><td>1</td><td>1.7</td></tr><tr><td>Grade 3 hypoalbuminaemia</td><td>4</td><td>8.7</td><td>8</td><td>15.4</td></tr><tr><td>Grade 4 hypoalbuminaemia</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>
Ulcerous bleeding: 3.3% (2/60)
Generalised oedema, ascites, or pleural effusion due to overhydration or hypoalbuminaemia: 21.7% (13/60)
Cardiovascular complications: 5% (3/60)
1 atrioventricular block and 2 ischaemic insults.
Puncture site complications: 3.3% (2/60)
Dissection of the common hepatic artery: 1/60
Femoral pseudoaneurysm: 1/60</td></tr>
<tr><td colspan="2">Abbreviations used: RECIST, Response evaluation criteria in solid tumours; CTCAE, Common Terminology Criteria for Adverse Events; IQR, interquartile range</td></tr>
</table>

Study 4 Abbott A (2018)

Details

Study type	**Non-randomised comparative study**
Country	USA
Recruitment period	2008 - 2014
Study population and number	**n=30** (6 Y90, 10 PHP, 12 CE, 1 PHP then CE, 1 CE then PHP) Patients with liver metastases from cutaneous or uveal melanoma.
Age and sex	Y90 = Age range, 30 to 90; 67% (4/6) male PHP = Age range, 30 to 90; 40 % (4/10) male CE = Age range, 30 to 90; 67 % (8/12) male
Patient selection criteria	Inclusion criteria: Above 18 years of age; Presented with cutaneous or uveal melanoma with metastatic disease to the liver and had regional therapy with PHP, Y90, or CE. Patients who had stable extrahepatic disease, defined as no evidence of progression on imaging studies, or prior surgical, regional, or systemic therapy for their disease were also included in the study.
Technique	Y90 treatment: all Y90 procedures were done using glass microspheres (TheraSphere; BTG International). Patients had either selective or lobar liver treatment based upon volume and distribution of disease. PHP treatment: PHP was done under general anaesthesia by both an interventional radiologist and a surgical oncologist using a double-balloon hepatic isolation and aspiration catheter and (Delcath Systems Inc.) and Melphalan. The median number of treatments received in this group was 3 (range, 1 to 6). CE was done by an interventional radiologist under conscious sedation by accessing the right common femoral artery. A mixture of doxorubicin, mitomycin C, and cisplatin emulsified with ethoidised oil (Lipiodol, Guerbet LLC, Bloomington, IN) was instilled in the lobe with the greatest volume of disease. Embolic particles were then added to the emulsification to create further stasis (Embosphere microspheres, Merit Medical).
Follow up	**Mean/median follow up – not reported**
Conflict of interest/source of funding	1 of the authors was on the medical advisory board for Delcath Systems and has grant and research support from Delcath Systems. The other authors declare no conflicts of interest.

Analysis

Study design issues: A single institution, retrospective review of patients with unresectable liver metastases from cutaneous or uveal melanoma treated with yttrium-90 (Y90), chemoembolisation (CE), or percutaneous hepatic perfusion (PHP) was conducted. Patients were selected from personal physician and departmental case-log databases. Demographic, clinical, treatments and outcomes data were retrieved from existing databases and electronic medical records. The patient records, tumour registry records, and the social security death index database were used to determine date of death. All images were reviewed by a single, board-certified radiologist to assess tumour burden and response to therapy or progression of disease based on RECIST. Tumour burden was defined as 0% to 25%, 25% to 50%, 50% to 75%, or >75% to allow for comparison among groups.

Fisher exact test was used to compared demographic and clinical variables. The Kaplan–Meier survival estimates, log-rank test, and multivariate Cox regression analysis (MVA) with time-dependent covariate were used to relate patient, tumour and treatment variables to HPFS, PFS, and OS. If a patient received >1 type of liver therapy, he or she was excluded from KM survival analysis but was included in MVA. HPFS and PFS were calculated at the time from first regional treatment until the first date of documented progression in the liver (HPFS) or overall progression (PFS). Overall PFS was defined as progression of disease at any site in the body, not limited to liver (that is, brain, liver, lung, nodal). OS was calculated from the date of first treatment until date of death or date of last follow up. All analyses were done in R.

IP overview: melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver

Study population issues: Among 30 patients included in the study, 16 had uveal, 13 cutaneous and 1 unknown primary melanoma. Treatment included 6 Y90 (5 uveal, 1 cutaneous), 10 PHP (3 uveal, 7 cutaneous), 12 CE (3 uveal, 9 cutaneous), 1 PHP then CE (uveal) and 1 CE then PHP (unknown). This difference in locations for the treatments was significant (p=0.002). There were no differences in sex, age, performance status, extrahepatic disease, tumour burden, adjuvant therapy use, prior hepatic treatment, or posttreatment complications between the groups.

Other issues: Some of the patients included in the PHP group from this study were also included in the RCT (Study 1).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30**

Survival Analysis

Survival Analysis	**Y90**	**CE**	**PHP**	***p***
Median HPFS (days)	54	80	361	0.001
Median PFS (days)	54	52	245	0.03
Median OS (days)	295	265	608	0.24

Multivariate analysis

Hepatic progression-free survival (HPFS)

Variables	**HR (95% CI)**	***P***
PHP vs Y90	0.11 (0.03-0.49)	0.004
PHP vs CE	0.31 (0.12-0.81)	0.02
CE vs Y90	0.36 (0.09-1.51)	0.17

Progression-free survival (PFS)

Variables	**HR (95% CI)**	***P***
PHP vs Y90	0.17 (0.04-0.63)	0.008
PHP vs CE	0.37 (0.14-0.94)	0.04
CE vs Y90	0.46 (0.13-1.65)	0.23

Overall survival (OS)

Variables	**HR (95% CI)**	***P***
PHP vs Y90	0.12 (0.02-0.78)	0.03
PHP vs CE	0.47 (0.17-1.25)	0.13
CE vs Y90	0.26 (0.05-1.34)	0.11

Safety

Complications by treatment groups

PHP = 60% (n=6)

Y90do = 100 % (n=6)

CE= 83% (n=10)

PHP then Y90= 100% (n=1)

CE then PHP = 100 % (n=1)

Most of the complications reported (all treatments) were anorexia, abdominal pain, fatigue and nausea, or emesis.

Thrombocytopenia and liver function test abnormalities were seen in some patients after the procedure, but they came back to baseline within a few days after treatment.

Abbreviations used: PHP, percutaneous hepatic perfusion; CE, chemoembolisation; Y90, yttrium-90 (Radioembolisation);HR, hazard ratio.

Study 5 Vogl T (2017)

Details

Study type	**Case series**
Country	Germany (multiple centres)
Recruitment period	2012 - 2016
Study population and number	**n=18** Patients with unresectable isolated hepatic metastases from uveal melanoma
Age and sex	Median: 55.5 years; 44.4 % (8/18) male
Patient selection criteria	Selection criteria (for the treatment): age >18 years, body weight[35 kg, surgically un-resectable hepatic metastases of uveal melanoma, no chemo-, radio- or biological therapy within 1 month prior PIHP, Eastern Cooperative Oncology Group performance status of 0–1, adequate hepatic (bilirubin <3 mg/dl), haematologic (platelet count >75,000/dl, haemoglobin[9 g/dl) and renal function (GFR >60 ml/min/1.73 m). Exclusion criteria (for the treatment): evidence of Child B or C cirrhosis, portal hypertension, congestive heart failure, chronic pulmonary restrictive disease, history of gastrinoma, Whipple procedure and bleeding disorders, known hypersensitivity to Melphalan or heparin, allergies to latex or iodinated contrast agent and pregnancy.
Technique	Delcath Hepatic CHEMOSAT Delivery System for Melphalan (Gen 2 filter) was used for the procedure. Treatment plan included one PIHP with the option of repeated treatment in cases of stable disease (SD) and partial response (PR). Patients with progressive disease (PD) did not receive further PIHP treatment. Median time between 1st and 2nd therapy was 63 days, from 2nd to 3rd was 134 days and from 3rd to 4th was 134 days. Dose of melphalan: 1st cycle: 2.5 mg/kg (range 1.8-3.2), 2nd cycle: 2.5 mg/kg (range 1.7-2.8), 3rd cycle: 2.8 mg/kg (range 2.7-2.8) and 4th cycle: 1.6 mg/kg.
Follow up	**Mean/median follow up – not reported**
Conflict of interest/source of funding	One author reported Grants from Siemens Healthcare, Promedicus Ltd., and Delcath Systems, Inc. and personal fees from Novartis Pharma GmbH. One author was an advisor and has received a speaker honorarium from Delcath Systems. No other CoI declared. No funding was received for this study.

Analysis

Study design issues: Retrospective, multicentre study on patients who had PIHP treatment for isolated metastatic liver disease from ocular melanoma. 18 patients were selected from 7 hospitals in Germany, who had 35 PIHP therapies. Median overall survival (OS) and median progression-free survival (PFS) were calculated. OS was defined as time from time from first PIHP to death. PFS was defined as time measured from first PIHP to documentation of progression or death. Tumour response was evaluated by means of RECIST 1.1 criteria. Peri- and postprocedural adverse events (AE) were reported. At 6 weeks after treatment, patients' life quality was assessed using four-point scale (1, very poor; 2, poor; 3, good; 4, very good) questionnaires (derived from short version of the validated checklist EORTC QLQ-C30 version 3).

Study population issues: All patients had a history of uveal melanoma and histologically proven, nonresectable metastases limited to the liver. 11 patients had prior therapy for hepatic metastases. Median age at 1st cycle was 55.5 years and median BMI was 25.3.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **18**

Tumour response

Response	**1st cycle (n=18)**	**2nd cycle (n=9)**	**3rd cycle (n=6)**	**4th cycle (n=2)**
CR (n)	0	0	0	0
PR (n)	44% (8)	89% (8)	83% (5)	0
SD (n)	39% (7)	0	17% (1)	0
PD (n)	17 % (3)	1 (11%)	0	100% (2)

Survival

Median OS = 9.6 months (range 1.6 – 41.0)

Median PFS = 12.4 months (range, 0.9-41.0)

One-year OS = 44%

Life-Quality questionnaire

	Pre-therapy scale (mean)	Post-therapy Response (Mean)
Overall health	2.3	3.3
Quality of life	2.3	3.6
Satisfaction with PIHP	-	3.8
Health change since therapy	-	2.3
Quality of life change since therapy	-	2.3

Safety

Adverse events (n=35 procedures)

Peri-procedural:

	N
Hypotension	2
Tachycardia	1
Coagulopathy	1
Ventricular fibrillation	1
Balloon rupture	1

Post-procedural (up to 30 days):

	N
Leukopenia	11
Thrombocytopenia	8
Fever	4
Oedema	2
Infection	2

Other post-procedural complications include (n=1 for each) anaemia, aneurysma spurium, ascites, asystole, bleeding, crisis of hypertension, epistaxis, haematemesis, hypoxia, inferior vena cava thrombosis, compartment syndrome (right leg) liver vein thrombosis, pleural effusion and vertigo.

Abbreviations used: OS, overall survival; PFS, progression-free survival: CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

Study 6 Artzner C (2019)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2015 - 2018
Study population and number	**n=16** Patients with liver-dominant metastatic uveal melanoma
Age and sex	Median 63.1 years; 62.5 % (10/16) Female.
Patient selection criteria	Patients who had CS-PHP for unresectable hepatic metastases of uveal melanoma between 2015 and 2018 were retrospectively selected from the institution.
Technique	Patients received melphalan using Delcath Hepatic CHEMOSAT® Delivery System. The median total procedure time was 3.5 h. Melphalan dose was 3.0 mg/kg ideal body weight (maximum dose 220 mg/treatment session).
Follow up	**Median: 6.13 months (IQR, 2.8 to 20.4 months)**
Conflict of interest/source of funding	Authors received no funding for this study. The authors declare that they have no competing interests.

Analysis

Follow-up issues: The median interval between baseline assessment and CS-PHP therapy was 8 days (interquartile range (IQR), 1 to 14 days). Follow-up imaging was scheduled every 3-months. The median interval between CS-PHP and follow-up imaging was 81 days (IQR, 50 to 94 days).

Study design issues: A retrospective, single-centre study investigating the effects of chemosaturation with PHP for liver-dominant metastatic uveal melanoma. 16 consecutive patients with unresectable hepatic metastasis were selected from single institution, who had 28 procedures in total. Image assessment was conducted by 2 radiologists. The response to therapy was characterised using RECIST 1.1. Readers were not blinded to clinical data. All data were reported as median and either total range or interquartile range. Kaplan–Meier estimators were used as non-parametric statistics to approximate the survival function.

Serious adverse events were categorised using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Electronic medical records were used for the SAE information. Median follow up regarding SAEs was 16 days (3 – 42 days).

Study population issues: Median age at first therapy was 63.1 years, median BMI was 26. All patients had metastatic lesions in both lobes of the liver. Median time between melanoma diagnosis and detection of hepatic metastasis was 2.4 years. The median time between diagnosis of hepatic metastases and first CS-PHP administration was 4.7 months. 8 patients (50%) had extrahepatic metastases before CS-PHP therapy (5 in bones, 4 in lungs, 1 in lymph nodes, 1 in spleen). 6 patients had prior systemic chemotherapy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **16**

Tumour response:

Response	**1st cycle (n=15)**	**2nd cycle (n=6)**	**3rd cycle (n=3)**
CR (n)	0	0	0
PR (n)	60% (9)	67% (4)	0
SD (n)	33% (5)	33% (2)	100% (3)
PD (n)	7 % (1)	0	0

1 patient received 4th, 5th and 6th cycle of CS-PHP that resulted in SD, SD, and PD Reponses, respectively.

Survival

Median Overall Survival = 27.4 months (95% CI 4.1-35.4)

One-year survival = 58%.

PFS after 1st cycle= 11.1 months (95% CI, 4.9-23.6)

PFS after 2nd cycle = 9.6 months (95% CI, 7.0-19.76)

Safety

Adverse events

1 patient had cardiac arrest during first CS-PHP therapy. He was treated with selective internal radiation therapy after successful treatment of a right coronary artery disease. He was removed from the subsequent analysis of the study.

AE	**N (%) (Grade 3/4)**	**N (%) (all grades)**
Anaemia	4 (14%)	27 (96%)
Leukopenia	4 (14%)	27 (96%)
Thrombocytopenia	4 (14%)	21 (75%)
Liver toxicity	0	13 (46%)
Vascular complication/Bleeding	0	2 (7%)
Nephrotoxicity	0	2 (7%)
Cardiovascular	1 (4%)	1 (4%)
Nausea and vomiting	0	17 (61%)
Infection/inflammation	0	5 (18%)
Capillary leak	0	1 (4%)

Abbreviations used: PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

Study 7 Marquardt S (2019)

Details

Study type	**Case series**
Country	9 countries in Europe (country lists not reported)
Recruitment period	2012-2016
Study population and number	**n=15** Patients with unresectable intrahepatic cholangiocarcinoma
Age and sex	Median 59 years; 53.3 % (8/15) Male
Patient selection criteria	Inclusion criteria: patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, with adequate haematological, renal and hepatic function (haemoglobin > 8 g/dl; leukocyte count > 2,000/µl; platelets > 50,000/µl, serum creatinine < 60 µmol/L, bilirubin ≤ 3 × upper limit of normal (ULN). Exclusion criteria (contraindications for the treatment): Distant extrahepatic metastases, recent history of transient ischaemic attacks, heart failure (left ventricular ejection fraction < 40%) or significant chronic obstructive or restrictive pulmonary disorder were considered contraindications for PHP.
Technique	Patients received melphalan using Delcath Hepatic CHEMOSAT® Delivery System (2nd Gen). The median procedure time was 177.5 min with a median melphalan dose of 188 mg. patients were planned for one PHP with the option of retreatment in case of stable disease (SD) or partial response (PR).
Follow up	**Mean follow up – not reported**
Conflict of interest/source of funding	The authors received no funding for this study. Several authors declared conflict of interest including travel grants, lecture fees, consulting and proctoring fees and personal fees from Delcath Systems Inc. Please refer to the study paper for detailed CoI declaration.

Analysis

Follow-up issues: Median time between 1st diagnosis and 1st PHP was 17.2 months (range 2-41.5) and median time between 1st and 2nd PHP was 3.2 months (range 2.1-4.2). 1 patient died before follow-up imaging at after 1st PHP, and 1 patient was lost to follow up after 5 PHP treatments.

Study design issues: Retrospective, multicentre study on safety and efficacy of PHP in 15 patients (26 procedures) from 9 different hospitals across Europe. Data were collected and evaluated locally, anonymised and submitted for retrospective evaluation. Outcome was measured according to RECIST 1.1. using CT or MRI every 3 months after PHP. Overall survival (OS) was calculated from initial diagnosis and first PHP until last follow up or death. Progression-free survival (PFS) was analysed from first PHP until first radiological intra- or extrahepatic progression, last follow up or death, whichever occurred first; hepatic progression-free survival (hPFS) was calculated in the same way but only for intrahepatic progression

Toxicity and peri-interventional complications were reported using the common terminology criteria for adverse events (CTCAE v4.03). Survival, including subgroup analysis, was assessed using the Kaplan–Meier estimation. The log rank test was used for to calculate differences and Mann-Whitney U test was used to test continuous data.

Study population issues: 4 patients had locoregional lymph node metastases. Before PHP therapy, 14 patients (93%) had systemic chemotherapy, 3 patients (20%) had transarterial therapy, 1 patient had hepatic resection, 1 had microwave ablation, 1 had SIRT, and 1 did not have any treatment.

Other issues: 3 patients from this study were also included in study 3.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **15**

Tumour response

Response	**1st cycle (n=15)**	**2nd cycle (n=5)**
CR (n)	7% (1)	0
PR (n)	13% (2)	20% (1)
SD (n)	53% (8)	60% (3)
PD (n)	20% (3)	20% (1)

1 patient died before follow-up imaging at 46 days after 1st PHP treatment due to sepsis and liver failure.

3rd, 4th and 5th treatment cycles were done in 2 patients with SD during long-term follow up.

Survival

Median OS from initial diagnosis = 26.9 months

Median OS from first PHP = 7.6 months

One-year OS from 1st PHP= 40%

Median PFS = 122 days

Median hPFS = 131 days

Subgroup analysis:

	Locoregional LN metastases	**Liver-only metastases**	***P***
Median OS from initial diagnosis	18.5 months	27.0 months	0.052
Median OS from 1st PHP	4.8 months	12.9 months	<0.01

Safety

Adverse events

Peri-procedural:

There were no AEs of grade 3 and 4 during the procedure. Hypotension and tachycardia were common during the hemofiltration but was controlled by medical management.

Post-procedural (n=26 procedures):

	N
Anaemia with need of transfusion	27 % (7)
Thrombocytopenia with need of transfusion	23% (6)
Leukopenia with need for G-CSF	15% (4)
Any haematological toxicity	35% (7)
Pneumonia**	15% (4)
Acute renal failure	4% (1)
Ascites	4% (1)
Bleeding	4% (1)
Oedema	4% (1)
Multi-organ failure/death*	4% (1)
Otitis	4% (1)
Pseudoaneurysm	4% (1)
Stroke (temporary)	4% (1)
Any non-haematological complications	35% (9)

*patient who had the highest tumour load in the liver (40%) developed acute multi-organ failure shortly after the treatment and despite intensive care treatment this patient died without tumour progression 46 days after PHP.

**The pneumonias were treated with antibiotics.

Abbreviations used: OS, overall survival; PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease. LN, lymph node; PHP, percutaneous hepatic perfusion.

Studies 8 and 9 Meijer T (2019 and 2020)

Details

Study type	**Case series**
Country	The Netherlands (single centre)
Recruitment period	2014-2017
Study population and number	**n=35** (64 procedures) patients with unresectable liver metastases from ocular melanoma
Age and sex	Median 59 years; 54.3% Female (19/35)
Patient selection criteria	Patients with unresectable, histologically confirmed, confined to liver metastases from ocular melanoma were included. Exclusion criteria: Age <18 or >75,Extrahepatic disease, WHO performance status ≥2, severe comorbidity precluding GA, Diabetes with nephropathy, Active infections,<40% healthy liver tissue, Other liver disease, Vascular anatomy impeding M-PHP, Intracranial lesions with propensity to bleed (on CT/MRI), Pregnancy. Exclusion criteria by lab test include: APTT and PT >1.5 x upper limit of normal (ULN); Leucocytes <3.0; Thrombocytes <100; Creatinine clearance <40 ml/min; AST, ALT, ALP, and LDH >2.5 x ULN; Bilirubin >1.5 x ULN.
Technique	Angiographic evaluation of the hepatic arteries was done 1 week before M-PHP. The Delcath Systems' second-generation filter was use for M-PHP treatment. All patients had 2 cycles of M-PHP at a 6–8-week interval (9 weeks in 1 patient) except in patients with progression of disease, unacceptable AEs or patient's reluctance. First M-PHPs were done with 3 mg melphalan/kg and a maximum dose of 220 mg. Second M-PHP dose was reduced with 20-25%. In total 67 procedures were done in 35 patients, with 92.5% (62/67) of the procedures were technically successful (completed treatment).
Follow up	**Median follow-up: 19 months**
Conflict of interest/source of funding	The study institution received financial support from Delcath System Inc for conducting M-PHP studies. The authors declared no conflict of interest.

Analysis

Follow-up issues:

Follow-up blood tests were done at 7, 9, 11, 14 and 16 days as well as at 4-8 weeks after the first and second cycle of treatment. Follow-up imaging was done at 4-8 weeks after the first and second M-PHP, every 3 months in the first year and every 6 months thereafter until disease progression.

In the 2020 study, there was no loss to follow up.

At baseline, 18 of 35 (51%) patients completed the EORTC QLQ-C30 v3.0 form. Return rates of the questionnaire at 6 weeks after the first M-PHP procedure, 6 weeks after the second M-PHP procedure, and 6 months after the first M-PHP procedure were 74% (26/35), 59% (17/29), and 49% (17/35), respectively.

Study design issues: A prospective, single-arm, single-centre phase 2 study. Histology specimens of liver metastases were obtained in all patients.

Primary endpoint for the 2019 study was number of serious adverse events (SAEs) occurring within 30 days after M-PHP, reported according to CTCAE v4.03. A SAE was defined as a serious complication resulting in death or life-threatening situation, prolonged hospital admission or readmission. Haematologic and hepatic toxicity were reported as early (0-3 days) and late events (days 4-30). SPSS was used for statistical analyses. Wilcoxon signed-rank test was used to compare pre- and post-treatment lab test results.

IP overview: melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver

Primary endpoints for the 2020 study were overall response rate and best overall response. Secondary endpoints included best hepatic response according to RECIST 1.1, overall survival, progression-free survival (PFS), hepatic PFS, safety and QoL.

OS was defined as time of first M-PHP until death or censoring. PFS and hepatic PFS were defined as time of first M-PHP until PD, death, or censoring.

Quality of life (QoL) was assessed using the EORTC QLQC30 v3.0 questionnaire. Questionnaires were filled out at baseline, 6 weeks after the first and second M-PHP, and 6 months after the first M-PHP.

Study population issues:

83% (29/35) of patients had 2 cycles of M-PHP, 17% (6/35) had only 1 cycle. 1 patient had 3 and 1 patient received 4 M-PHPs. Prior therapy for liver metastasis included systemic therapy (n=8), regional therapy (n=4), regional and systemic therapy (n=2) and no therapy (n=21).

Only 91% (32/35) of patients were analysed. In 2 patients, a therapeutic melphalan dose could not be administered due to peri-procedural complications and therefore no treatment effect could be evaluated. In 1 patient, target lesions were absent (all lesions with maximal diameter of less than 1 cm).

Other issues:

Key efficacy and safety findings

Efficacy (from the 2020 study)

Number of patients analysed: 32

Overall response rate: 72% (23/32)

Confirmed hepatic response rate: 81% (n=26)

Best overall response and best hepatic response

	Best overall response		Best hepatic response	
	All evaluable patients	Patients with 2 M-PHPs	All evaluable patients	Patients with 2 M-PHPs
CR	3% (1/32)	4% (1/27)	3% (1/32)	4% (1/27)
PR	69% (22/32)	70% (19/27)	78% (25/32)	82% (22/27)
SD	13% (4/32)	11% (3/27)	19% (6/32)	15% (4/27)
PD	16% (5/32)	15% (4/27)	0%	0%

Five patients had PD as best overall response due to extrahepatic metastases; the sum of target lesions in the liver remained stable (n=3) or decreased by more than 30% (n=2).

Survival analysis

After a median follow up of 19 months, 17% (6/35) of patients were still alive.

One-year OS=77%

Two-year OS=43%

Median OS was 19.1 months for all included patients (n=35)

Safety (from the 2019 study)

Serious adverse events:

A total of 14 serious adverse events were reported.

	N
Transient cardiac ischaemia	1
Periprocedural difficulties with oxygenation	1
Post-procedural hypotension (asymptomatic)	1
Post-procedural ECG changes (asymptomatic)	1
Pulmonary emboli	2
Nausea/vomiting with mild hypokalaemia	1
Sepsis with bacterial pharyngitis and retropharyngeal abscess	1
Vaginal haemorrhage with grade 2 anaemia	1
Febrile neutropenia	2
Febrile neutropenia with mucositis/esophagitis	1
Prostatitis	1
Abdominal pain (unknown cause)	1
Total	14

IP overview: melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver

Median OS according to best overall response:

27.5 months (95% CI 23.7 to 31.3) for patients with CR/PR

14.2 months (95% CI 11.4 to 17.0) for patients with SD

9.1 months (95% CI 5.5 to 12.8) for patients with PD.

It was statistically significantly longer in patients whose disease responded than in those whose disease did not respond (27.5 months compared with 11.9 months. p<0.001).

Univariate analysis showed that the presence of a liver metastasis with diameter ≥ 3 cm (p = 0.01) and an elevated baseline lactate dehydrogenase (LDH; 248 U/L, p = 0.03) were statistically significantly associated with a poorer OS.

Median PFS: 7.6 months (95% CI 4.9 to 10.3)

Median hepatic PFS: 11.2 months (95% CI: 9.0 to 13.4)

One-year PFS: 26.5%

59% (20/34) of patients who eventually showed PD during the study received one or more subsequent treatments.

74% (26/35) of patients developed extrahepatic metastases during follow up.

QoL (EORTC QLQ-C30 v3.0 form)

	Before treatment Median (range)	6 weeks after 1st M-PHP Median (range)	6 weeks after 2nd M-PHP Median (range)	6 months after 1st M-PHP Median (range)
Global health status/QoL (0–100)	83 (33–100)	83 (33–100)	83 (42–100)	83 (25–100)

Questionnaire scores after treatment did not significantly differ from scores before treatment, except for physical functioning which was statistically significantly impaired 6 weeks after the second M-PHP (p=0.011). The level of physical functioning was restored to normal 3 months later.

Transient cardiac ischaemia occurred during the procedure and resolved without any sequelae. There were 5 cases of prolonged hospital stays (4-5 days) and 8 readmissions.

Haematologic toxicity (0-30 days)

	% (n)
Grade 3/4 anaemia	18.1 % (6)
Grade 3/4 thrombocytopenia	54.5% (18)
Grade 3/4 leukopenia	75.6% (25)
Grade 3/4 neutropenia	66.7% (22)
Grade 3/4 lymphocytopenia	84.8% (28)

Other complications

	n
Post-procedural haemorrhage	11
Generalised oedema and/or pleural effusion	8
Fever	7
Nausea	7
Abdominal pain	4
Alopecia	3
Diarrhoea	2

Other reported adverse events (n=1 for each) were bladder infection, cystitis, upper respiratory infection, vulva infection and hyperglycaemia.

Abbreviations used: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organisation for Research and Treatment of Cancer; LDH, lactate dehydrogenase; M-PHP, percutaneous hepatic perfusion with melphalan; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QoL, quality of life; SD, stable disease.

Study 10 Vogl TJ (2014)

Details

Study type	**Case series**
Country	Germany, Italy
Recruitment period	2012 - 2013
Study population and number	**n=14 (13 patients treated with PHP)** Patients with unresectable hepatic metastases from solid tumours
Age and sex	Median 54 years; 50% (7/14) male
Patient selection criteria	Not reported
Technique	Before therapy, a complete visceral angiogram was done to examine vascular anatomy, embolisation of selected arterial branches supplying GI tract was done. Patients received melphalan delivered using the Delcath Hepatic CHEMOSAT® delivery system. 1st generation filter was used in 3 patients, 2nd generation filters were used in 7 patients and 3 patients received 1st then 2nd for repeat treatments. Melphalan was given at a dose of 3.0 mg/kg ideal body weight (maximum 220 mg/treatment).
Follow up	**Mean/median follow up – not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: CT, MRI and/or PET scans of the liver were done at 4- to 8-week intervals.

Study design issues: Retrospective data analysis of 14 consecutive patients from 2 institutions in Europe who had chemosaturation-PHP for unresectable hepatic metastases from various solid tumours. Tumour response of liver lesions was assessed using RECIST criteria. Systemic and local adverse events were classified by the CTCAE version 3.0. Only systemic events and hepatic transaminases which did not resolved with 24 hours were reported. No statistical analyses were done. Of the 14 patients, 13 received PHP (total 18 treatments), but only 12 patients were evaluated for tumour response.

Study population issues: Patients had ocular (n = 8) or cutaneous melanoma (n = 3), breast cancer (n = 1), gastric cancer (n = 1) and cholangiocarcinoma (n = 1). All patients, except for 1, had metastases confined to the liver. Prior treatment included transarterial chemoembolisation (n=5), systemic chemotherapy (n=10), hepatic resection (n=4), microwave ablation (n=1), selective internal radiotherapy (n=1) and radiofrequency ablation (n=2).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 12
2 out of 14 patients recruited were not evaluated for tumour response because the procedure was abandoned in 1 patient due to vaginal bleeding and another patient died shortly after treatment.

Tumour response
<table>
<tr><td></td><td>n</td></tr>
<tr><td>Complete response</td><td>1 (8.3%)</td></tr>
<tr><td>Partial response</td><td>6 (50.0%)</td></tr>
<tr><td>Stable disease</td><td>5 (41.7%)</td></tr>
</table>
</td><td>
Toxicity
<table>
<tr><th>Toxicity (all grades)</th><th>1st gen filter(n=6)</th><th>2nd gen filter(n=10)</th><th>Total (n=18 procedures)</th></tr>
<tr><td>Anaemia</td><td>6</td><td>7</td><td>13 (72.2%)</td></tr>
<tr><td>Thrombocytopenia</td><td>6</td><td>4</td><td>10 (55.5%)</td></tr>
<tr><td>Leukocytopenia</td><td>6</td><td>4</td><td>10 (55.5%)</td></tr>
<tr><td>Transaminitis</td><td>2</td><td>0</td><td>2 (11.1%)</td></tr>
</table>
Other complications
<table>
<tr><td></td><td>n</td></tr>
<tr><td>Febrile neutropenia</td><td>2</td></tr>
<tr><td>Fatigue</td><td>7</td></tr>
<tr><td>Nauseas</td><td>2</td></tr>
<tr><td>Vaginal bleeding (heparin induced) *</td><td>1</td></tr>
<tr><td>Retroperitoneal giant hematoma</td><td>1</td></tr>
</table>
* The patient recovered without sequelae. This patient did not go on to receive chemosaturation with PHP.

Death
The patient who had giant retroperitoneal hematoma died 30 hours after chemosaturation with PHP.
</td></tr>
<tr><td colspan="2">Abbreviations used: RECIST, Response evaluation criteria in solid tumours; CTCAE, Common Terminology Criteria for Adverse Events; PHP, percutaneous hepatic perfusion</td></tr>
</table>

Study 11 Brüning R (2020)

Details

Study type	**Retrospective case series**
Country	Germany (single centre)
Recruitment period	2014 to 2019
Study population and number	**n=19** patients with unresectable hepatic metastases from ocular melanoma treated with 43 PHP-M (median 2 PHP-M)
Age and sex	Mean 58 years; 58% (11/19) male
Patient selection criteria	Inclusion criteria: Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and with adequate haematologic, renal, and hepatic function data. Exclusion criteria: distant extrahepatic metastasis exceeding 10mm in lymph nodes or in relevant other locations, recent history of transient ischaemic attacks, heart failure, contraindications to general anaesthesia, or significant chronic obstructive or restrictive pulmonary disorders.
Technique	PHP-M Device used: CHEMOSAT® Second Generation; Delcath Systems Inc., New York, NY, USA The interval between first and second PHP was on average of 119 days (SD of 145 days).
Follow up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The patients had to have at least 1 follow up including an MRI- or CT-based restaging; patients lost to follow up were not included in this evaluation (n=1).

Study design issues: Tumour response and adverse events were evaluated using RECIST1.1 and the Clavien–Dindo classification. Kaplan–Meier methods and Cox regression hazard proportional models were used.

Study population issues:

Seven patients received previous systemic treatment, 4 patients received transarterial chemoembolisation or transarterial chemoperfusion and 3 patients received previous surgical or ablative therapy, and these therapies were terminated for either side effects or progressive disease. Six patients had no specified previous therapy.

At baseline, 10 patients had a partial remission and 9 patients had stable disease.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 19

Survival
Median OS following initial diagnosis: 26.4 months
Median OS following first PHP-M treatment: 16.7 months
PFS since first imaging: 751.8 days ± 515.5 years
PFS since first PHP: 427.8 ± 295.2 days
Estimated OS from first imaging to 5 years: 0.213 (95% CI 0.0449 to 1)
Estimated OS at 1 year after chemosaturation: 0.793 (95% CI 0.609 to 1)
Estimated OS at 2 years after chemosaturation: 0.604 (95% CI 0.380 to 0.960)

Increased OS was associated with lower tumour volume (hazard ratio [95% confidence interval] for tumour volume as stratified in 10mL versus 150 mL: 0.190 [0.041 to 0.893], p<0.05).

Tumour response following the initial treatment
<table>
<tr><th></th><th>n</th></tr>
<tr><td>Complete response</td><td>0</td></tr>
<tr><td>Partial response</td><td>53% (10/19)</td></tr>
<tr><td>Stable disease</td><td>47% (9/19)</td></tr>
<tr><td>Progressive disease</td><td>0</td></tr>
</table>
</td><td>
Adverse events (Clavien-Dindo classification)
n=43 procedures
<table>
<tr><th></th><th>n</th><th>Detail</th></tr>
<tr><td>Grade ≤ 1</td><td>0</td><td>-</td></tr>
<tr><td>Grade 2</td><td>1</td><td>-</td></tr>
<tr><td>Grade 3A</td><td>2</td><td>Coronary ischaemia</td></tr>
<tr><td>Grade 3B</td><td>1</td><td>Transfemoral bleeding with following surgery</td></tr>
<tr><td>Grade 4 or 5</td><td>0</td><td></td></tr>
<tr><td>Total</td><td>4</td><td></td></tr>
</table>
There were changes in the haematological state, most strongly in platelet count (from 251.7/nL (SD 65.8) before the first PHP-M procedure to an average of 104.2/nL (SD 45.4) following the procedure).
Bilirubin following the procedure was stable at an average of 0.9 (SD 0.6).
Erythrocytes following the procedure were stable at 4.1/pL (SD 0.5).
</td></tr>
<tr><td colspan="2">Abbreviations used: RECIST, Response evaluation criteria in solid tumours; OS, overall survival; PFS, progression-free survival; PHP-M, percutaneous hepatic perfusion with melphalan</td></tr>
</table>

Validity and generalisability of the studies

- Most of the studies are retrospective case series with small sample sizes. Only 1 RCT is included, which had 93 patients. One prospective study is also included.
- No meta-analysis or systematic review with pooled analysis was found in the literature in this topic area.
- Apart from the RCT, all the other studies used second-generation Delcath filters for the chemosaturation.
- All studies used melphalan as the chemotherapeutic agent.
- Studies are heterogenous in terms of type of tumour and origin of the metastases. Eiqht studies (including 2 with the same patients) had patients with ocular or cutaneous melanoma origin, 1 study had metastasis origin from any solid tumours, 1 study had cholangiocarcinoma patients and 1 study had both primary and secondary liver tumours (including hepatic metastases from ocular melanoma).
- Some studies excluded extrahepatic metastatic diseases, others did not.

Existing assessments of this procedure

NHS England Specialised Commissioning Team has published a clinical commissioning policy on chemosaturation for liver metastases from ocular melanomas in 2016. Evidence review for the policy document included 2 case series and the previous NICE guidance on this topic. The policy statement concluded that there is not enough evidence to support a proposal for the routine commissioning of chemosaturation for liver metastases from ocular melanomas.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Irreversible electroporation for primary liver cancer. Interventional procedures guidance 664 (2019). Available from https://www.nice.org.uk/guidance/ipg664
- Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma. NICE interventional procedures guidance 630 (2018). Available from https://www.nice.org.uk/guidance/IPG630
- Microwave ablation for treating liver metastases. NICE interventional procedures guidance 553 (2016). Available from https://www.nice.org.uk/guidance/ipg553
- Selective internal radiation therapy for primary hepatocellular carcinoma. NICE interventional procedures guidance 460 (2013). Available from https://www.nice.org.uk/guidance/ipg460
- Irreversible electroporation for treating liver metastases. Interventional procedures guidance 445 (2013). Available from https://www.nice.org.uk/guidance/ipg445
- Selective internal radiation therapy for non-resectable colorectal metastases in the liver. Interventional procedures guidance 401 (2011). Available from https://www.nice.org.uk/guidance/ipg401
- Cryotherapy for the treatment of liver metastases. Interventional procedures guidance 369 (2010). Available from https://www.nice.org.uk/guidance/ipg369
- Microwave ablation of hepatocellular carcinoma. Interventional procedures guidance 214 (2007). Available from https://www.nice.org.uk/guidance/ipg214

Technology appraisals

- Regorafenib for previously treated advanced hepatocellular carcinoma. NICE technology appraisal guidance 514 (2018). Available from http://www.nice.org.uk/guidance/TA514

- Sorafenib for treating advanced hepatocellular carcinoma. NICE technology appraisal guidance 474 (2017). Available from http://www.nice.org.uk/guidance/ta474

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. No Professional expert questionnaires for 'melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver' were submitted.

Patient commentators' opinions

NICE received 1 submission from a patient organisation.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- In an attempt to reduce haematologic toxicity, various modifications were made to the original first-generation filter of the Delcath CHEMOSAT System, resulting in second-generation filter that became commercially available since 2012.

- Although the literature review was not restricted to any period, only the most recent studies were selected for this overview, taking into consideration the

change in filter. Therefore, all but 1 study from this overview involved second-generation filters.

- Ongoing trials:

  - Percutaneous Hepatic Perfusion in Patients With Hepatic-dominant Ocular Melanoma (FOCUS); NCT02678572; Multi-centre, single-arm ,open-label study; US and Europe (including 2 UK centres); Estimated enrolment: 80; Study start date: Feb 2016; estimated study completion date: June 2020.

  - Percutaneous Hepatic Perfusion vs. Cisplatin/Gemcitabine in Patients with Intrahepatic Cholangiocarcinoma; NCT03086993; RCT; US; estimated enrolment 295; Study start date: April 2018; Estimated completion date May 2023.

  - Collection of safety, efficacy and resource utilization information in patients who have received melphalan PHP with the Delcath Hepatic Delivery System for the treatment of unresectable hepatic malignancy; NCT03266042; Registry study; UK; Estimated enrolment 200; estimated completion date: February 2020.

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6. Artzner C, Mossakowski O, Hefferman G, et al. (2019) Chemosaturation with percutaneous hepatic perfusion of melphalan for liver-dominant metastatic uveal melanoma: a single center experience. Cancer Imaging;19(1):31.
7. Marquardt S, Kirstein M, Brüning R et al. (2019) Percutaneous hepatic perfusion (chemosaturation) with melphalan in patients with intrahepatic cholangiocarcinoma: European multicentre study on safety, short-term effects and survival. Eur Radiol 29, 1882–1892.
8. Meijer T, Burgmans M, Fiocco M et al. (2019) Safety of Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Liver Metastases from Ocular Melanoma Using the Delcath Systems' Second-Generation Hemofiltration System: A Prospective Non-Randomized Phase II Trial. Cardiovasc Intervent Radiol 42, 841–852.
9. Meijer TS, Burgmans MC, de Leede EM, et al (2020) percutaneous hepatic perfusion with melphalan in patients with unresectable ocular melanoma metastases confined to the liver: a prospective phase ii study [published online ahead of print]. Ann Surg Oncol. 2020;10.1245/s10434-020-08741-x.
10. Vogl T, Zangos S, Scholtz J et al. (2014). Chemosaturation with Percutaneous Hepatic Perfusions of Melphalan for Hepatic Metastases:

Experience from Two European Centers. Röfo - Fortschritte Auf Dem Gebiet Der Röntgenstrahlen Und Der Bildgebenden Verfahren, 186(10), 937-944.

11. Brüning R, Tiede M, Schneider M, et al. Unresectable Hepatic Metastasis of Uveal Melanoma: Hepatic Chemosaturation with High-Dose Melphalan-Long-Term Overall Survival Negatively Correlates with Tumor Burden. Radiol Res Pract. 2020;2020:5672048. Published 2020 Sep 2. doi:10.1155/2020/5672048.

Literature search strategy

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	10/08/2020	Issue 8 of 12, August 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	10/08/2020	Issue 8 of 12, August 2020
MEDLINE (Ovid)	10/08/2020	1946 to August 07, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	10/08/2020	August 07, 2020
EMBASE (Ovid)	10/08/2020	1974 to 2020 August 07

MEDLINE search strategy

1 Liver Neoplasms/ (148090)
2 ((liver or hepatic* or hepatocell*) adj4 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metastas*)).tw. (149353)
3 (hepatoma* or cholangiocarcinoma* or hepatocarcinoma* or HCC).tw. (81569)
4 1 or 2 or 3 (222060)
5 Chemotherapy, Cancer, Regional Perfusion/ (3768)
6 ((Percut* or isolate*) adj4 (hepat* or liver*) adj4 (perfus* or chemoperfus*)).tw. (4676)
7 CS-PHP.tw. (6)
8 PHP.tw. (1677)
9 PIHP.tw. (27)
10 Chemosat*.tw. (12)
11 Melphalan.tw. (7129)
12 Delcath.tw. (9)
13 ((Hepat* or liver*) adj4 (vein* or venous* or arter* or outflow*) adj4 (isolat* or segregate*)).tw. (254)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (16688)
15 4 and 14 (819)

16 animals/ not humans/ (4690867)
17 15 not 16 (681)

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Case reports have been excluded unless they describe a safety event that has not been described in the table 2 studies.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Burgmans MC, de Leede EM, Martini CH et al. (2016) Percutaneous isolated hepatic perfusion for the treatment of unresectable liver malignancies. Cardiovasc Intervent Radiol;39(6):801–814.	Review	PHP is a novel, minimally invasive, and repeatable alternative to IHP. Phase 1 studies have demonstrated PHP to be feasible and safe. A recent RCT has shown improved control of liver disease compared to standard available therapy in patients with hepatic metastases from (ocular) melanoma.	Review
Curley SA, Newman RA, Dougherty TB et al. (1994) Complete hepatic venous isolation and extracorporeal chemofiltration as treatment for human hepatocellular carcinoma: a phase I study. Annals of Surgical Oncology 1: 389-399	Case series n=10	Peak systemic doxorubicin levels were an average 86% lower than were peak prefilter levels ($p<0.01$). Because all catheters were placed percutaneously and because the chemofiltration markedly limited systemic chemotherapy exposure, patients were discharged 1 day after 16 of the 17 treatments.	Larger, more recent studies are included.
de Leede E, Burgmans M, Meijer T et al. (2017) Prospective Clinical and Pharmacological Evaluation of the Delcath System's Second-Generation (GEN2) Hemofiltration System in Patients Undergoing Percutaneous Hepatic Perfusion with Melphalan. Cardiovasc	Case series n=10	The study analysed he pharmacokinetics and toxicity of PHP using the new GEN2 filter. The analysis of blood samples showed an overall filter efficiency of 86%. Mean filter efficiency decreased from 95.4% 10 min after the start of melphalan infusion to 77.5% at the end of the procedure (p	Study on filter efficiency (pharmacokinetics). Not relevant.

Intervent Radiol 40, 1196–1205		= 0.051). Bone marrow depression was seen after up to 80.0% of 10 procedures but was self-limiting.	
Fitzpatrick M, Richard Alexander H, Deshpande S et al.(2014). Use of Partial Venovenous Cardiopulmonary Bypass in Percutaneous Hepatic Perfusion for Patients with Diffuse, Isolated Liver Metastases: A Case Series. Journal of Cardiothoracic and Vascular Anesthesia, 28(3), 647-651	Case series n=5 (total 15 PHPs)	Peripheral hepatic perfusion is a novel and effective method of treating diffuse isolated liver metastases while minimising systemic side effects.	Larger studies are included.
Forster M, Rashid O, Perez M et al. (2014) Chemosaturation with percutaneous hepatic perfusion for unresectable metastatic melanoma or sarcoma to the liver: a single institution experience. J Surg Oncol;109(5):434–439.	Case series n=10 Patients with unresectable melanoma or sarcoma hepatic metastasis treated with PHP.	Median hPFS was 240 days, 9 of 10 patients (90%) demonstrated stable disease or partial response to treatment. Myelosuppression was the most common morbidity.	Larger studies are included.
Fukumoto T, Tominaga M, Kido M et al (2014). Long-Term Outcomes and Prognostic Factors with Reductive Hepatectomy and Sequential Percutaneous Isolated Hepatic Perfusion for Multiple Bilobar Hepatocellular Carcinoma. Ann Surg Oncol 21, 971–978	Case series n=68 Patients with intermediate or advanced hepatocellular carcinoma (HCC).	Patients had reductive hepatectomy and PIHP with mitomycin C. The objective response rate of PIHP was 70.6 % (complete plus partial response). The median OS of all 68 patients was 25 months, and the 5-year OS rate was 27.6 %.	PHP treatment was combined with reductive surgery in HCC patients. Not relevant.
Glazer ES, & Zager JS (2017). Chemosaturation with Percutaneous Hepatic Perfusion in Unresectable Hepatic Metastases. Cancer Control, 96–101.	Review n=91	Chemosaturation with percutaneous hepatic perfusion produces favourable tumour response rates in select individuals with unresectable hepatic metastases from multiple primary cancers, particularly ocular and cutaneous melanomas.	Review

Hwu WJ, Salem RR, Pollak J et al. (1999) A clinical-pharmacological evaluation of percutaneous isolated hepatic infusion of doxorubicin in patients with unresectable liver tumors. Oncology Research 11: 529-537	Case series n=18 (12 evaluable for disease response)	There were 4 partial responses, 3 minor responses, 1 stable disease, and 4 progressive disease. The median overall survival of responders was 23 months, and for non-responders it was 8 months.	Larger, more recent studies are included.
Kirstein M, Marquardt S, Jedicke N et al. (2017) Safety and efficacy of chemosaturation in patients with primary and secondary liver tumors. J Cancer Res Clin Oncol 143, 2113–2121.	Case series n=29	Second-generation CS-PHP seems to be effective and tolerable. Patient selection based on tumour volume and entity is of importance. Particularly, patients with ocular melanoma and hepatobiliary tumours represent promising candidates for CS-PHP.	All patients are included in the Schönfeld L (2020) study (study 3).
Ku Y, Iwasaki T, Fukumoto T et al. (1998) Percutaneous isolated liver chemoperfusion for treatment of unresectable malignant liver tumors: technique, pharmacokinetics, clinical results. Recent Results in Cancer Research 147: 67–82	Case series n=46	Of the 27 evaluable HCC patients, 17 (63%) had an objective tumour response (5 complete and 12 partial responses). In 15 patients with colorectal hepatic metastases (CHM), 7 had a sharp decrease in serum carcinoembryonic antigen (CEA) levels (to < 50% of their pre-treatment levels) after treatment. The results indicate that PILP with HVI-CHP has high efficacy in most patients with multiple advanced liver tumours	Included in the overview for the previous guidance.
Miao N, Pingpank JF, Alexander HR et al. (2008) Percutaneous hepatic perfusion in patients with metastatic liver cancer: anesthetic, hemodynamic, and metabolic considerations. Annals of Surgical Oncology 15: 815-823	Case series n=51	Percutaneous hepatic perfusion therapy can be associated with transient but significant hemodynamic and metabolic perturbations. In order to assure patient comfort and facilitate timely diagnosis and treatment of associated hemodynamic and metabolic changes, we favour administration of	The study focuses on anaesthetic, haemodynamic and metabolic aspects of the procedure.

		general anaesthesia, rather than sedation, for patients having PHP	
Pingpank JF, Libutti SK, Chang R et al. (2005) Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. Journal of Clinical Oncology 23: 3465–74	Case series n=28	An overall radiographic response rate of 30% was observed in treated patients. In the 10 patients with ocular melanoma, a 50% overall response rate was observed, including 2 complete responses. Transient grade 3/4 hepatic and systemic toxicity was seen after 19% and 66% of treatments, respectively.	Included in the overview for the previous guidance.
Ravikumar TS, Pizzorno G, Bodden W et al. (1994) Percutaneous hepatic vein isolation and high-dose hepatic arterial infusion chemotherapy for unresectable liver tumors. Journal of Clinical Oncology 12: 2723–36	Case series n=23	The use of a double-balloon catheter to isolate and detoxify hepatic venous blood during intraarterial therapy is technically feasible, safe, and allows administration of large doses of intrahepatic chemotherapy at short intervals.	Included in the overview for the previous guidance.
Vogel A, Gupta S, Zeile M et al. (2017) Chemosaturation Percutaneous Hepatic Perfusion: A Systematic Review. Adv Ther ;33(12):2122–2138.	Review	Chemosaturation percutaneous hepatic perfusion (CS-PHP) is an effective regional treatment option for patients with unresectable primary or hepatic metastases. The toxicities associated with CS-PHP are in most cases transient and manageable.	Review
Yamamoto M, & Zager J (2013). Isolated hepatic perfusion for metastatic melanoma. Journal of Surgical Oncology, 109(4), 383-388.	Review	Isolated Hepatic Perfusion (IHP) remains the gold standard for hepatic whole organ perfusion therapy, with PHP building on the isolation and saturation principles using a minimally invasive and percutaneous approach. Both IHP and PHP offer the patient with metastatic ocular or	Review

		cutaneous melanoma to the liver treatment options that have relatively high and durable regional response rates.	