Cancer may develop in the liver (primary cancer) or may spread there from other tissues (metastatic cancer). When chemotherapy drugs are used to treat these cancers they can cause side effects because they reach other parts of the body. In this procedure the blood flow from the liver to the rest of the body is temporarily stopped while the chemotherapy drugs are given directly into the liver blood vessels. The blood in the liver is then drained away and filtered before reconnecting the normal blood flow: this aims to protect the rest of the body from the side effects of the chemotherapy.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this 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 specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2013.

Procedure name

- Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

Specialist societies

- British Society of Interventional Radiology
- Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland
Description

**Indications and current treatment**

The most common types of primary liver cancer are hepatocellular carcinoma (also known as hepatoma) and cholangiocarcinoma. However, cancer occurs more often as a result of metastases from other sites such as the lung, colon and stomach.

Treatment for primary or metastatic liver cancer depends on the location and stage of the cancer and how well liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation and selective internal radiation therapy. Liver transplantation may be appropriate for some patients. In patients with primary liver cancer, surgical removal with curative intent 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 is not new and was originally carried out by open surgical techniques. This carried a risk of significant mortality and morbidity and has been replaced by a completely percutaneous method. This may make the procedure safer and unlike the surgical approach can be repeated.

**What the procedure involves**

The aim of chemosaturation (via percutaneous hepatic perfusion and hepatic vein isolation) is to improve hepatic progression-free survival by delivering a very high dose of chemotherapy directly into the arterial supply of the liver. The blood within the liver is then removed briefly from the body via a special catheter, filtered to remove the drug and then infused back into the circulation. This prevents what would be a lethal dose of chemotherapy reaching the rest of the body.

The procedure is usually done under general anaesthesia. A catheter is first manipulated into the hepatic artery in a position such that the tumour is appropriately targeted. The internal jugular and femoral veins are then catheterised using ultrasound guidance. A multi-lumen, double-balloon catheter is inserted via the femoral vein into the inferior vena cava, and across the hepatic veins. The balloons are inflated such that the hepatic venous outflow is completely isolated from the systemic circulation. The blood then exits the liver through a channel in the multilumen catheter into an extracorporeal filtration system. This extracts most of the chemotherapy drug before returning the filtered blood back into the circulation through the internal jugular vein. The duration of the chemotherapy infusion into the hepatic artery

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IP overview: Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

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is around 30 minutes. Full anticoagulation with heparin is required throughout the procedure.

There is often a significant change in the patient’s haemodynamics during the procedure due to the extracorporeal filtration process and an anaesthetist and perfusion specialist are required to support the patient.

In order to improve the safety of the procedure some specialists now advocate a first stage where the arterial circulation is checked with an angiogram and any branches near the liver supplying other structures e.g. stomach embolised to prevent the chemotherapy reaching these organs and causing damage. This is similar to what is done prior to SIRT (selective internal radiotherapy).

**Outcome measures**

The ‘Response evaluation criteria in solid tumors’ (RECIST) are used for measuring tumour response using X-ray, CT and magnetic resonance imaging (MRI). There are four 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.

**Literature review**

**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 of the liver. Searches were conducted of the following databases, covering the period from their commencement to 26 September 2013: 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 appendix C for details of 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication type</td>
<td>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.</td>
</tr>
<tr>
<td>Patient</td>
<td>Patients with primary or metastatic liver cancer.</td>
</tr>
<tr>
<td>Intervention/test</td>
<td>Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.</td>
</tr>
<tr>
<td>Language</td>
<td>Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.</td>
</tr>
</tbody>
</table>

**List of studies included in the overview**

This overview is based on approximately 243 patients from 5 case series\(^1\text{-}^5\).

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.
Table 2 Summary of key efficacy and safety findings on chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

<table>
<thead>
<tr>
<th>Study details</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pingpank JF (2005)†</td>
<td>Number of patients analysed: 27</td>
<td>Complications:</td>
<td>Follow-up issues:</td>
</tr>
<tr>
<td>Case series (prospective)</td>
<td>Overall radiographic response rate=29.6% (8/27) (6 partial response and 2 complete response) In addition, there were 10 patients with minor responses.</td>
<td>- Pneumothora, n=1</td>
<td>1 patient withdrew from the study after 1 treatment and is included in the toxicity assessment only.</td>
</tr>
<tr>
<td></td>
<td>Patients with metastatic ocular melanoma (n=10)</td>
<td>- Arterial puncture, n=1</td>
<td>All patients were followed up until disease progression with physical examination, laboratory tests, CT scan of the chest, abdomen and pelvis, and MRI of the liver every 3 months for the first year and every 4 months thereafter.</td>
</tr>
<tr>
<td></td>
<td>- Partial response=30% (3/10)</td>
<td>- Cervical haematoma, n=1</td>
<td>Study design issues:</td>
</tr>
<tr>
<td></td>
<td>- Complete response=20% (2/10)</td>
<td>- Hepatic artery dissection, n=1</td>
<td>- Phase I study</td>
</tr>
<tr>
<td></td>
<td>- Minor response=30% (3/10)</td>
<td>- Intratumour haemorrhage, n=1</td>
<td>- The purpose of the study was to demonstrate feasibility in an initial cohort and subsequently determine the maximum tolerated dose and dose-limiting toxicity of melphalan.</td>
</tr>
<tr>
<td></td>
<td>The duration of partial responses includes 2 patients with ongoing responses at 9 and 11 months, respectively. Duration of the 2 complete responses was 10 and 12 months, respectively.</td>
<td>- Protamine reaction, n=1</td>
<td>- Response and duration of response were scored only for lesions in the liver.</td>
</tr>
<tr>
<td></td>
<td>Patients with progressing hepatic metastases from pancreatic neuroendocrine tumours (n=4)</td>
<td>- Heparin-induced thrombocytopaenia, n=1</td>
<td>Study population issues:</td>
</tr>
<tr>
<td></td>
<td>- Ongoing partial response in 2 patients at 5 and 7 months, respectively. In both patients, response was correlated with symptom relief and decreased hormone levels.</td>
<td></td>
<td>- Most patients had received previous treatment for hepatic metastases (13 systemic chemotherapy, 7 regional chemotherapy, 4 resection, 2 radiofrequency ablation).</td>
</tr>
<tr>
<td></td>
<td>- Ongoing minor response at 10 months.</td>
<td></td>
<td>Other issues:</td>
</tr>
<tr>
<td>n=28</td>
<td></td>
<td></td>
<td>- Patients with evidence of disease progression on interval evaluation were not offered additional treatments. A single patient was re-enrolled on the trial after disease recrudescence following prolonged complete response (10 months).</td>
</tr>
<tr>
<td>Age: mean 49 years (range 17–74)</td>
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<tr>
<td>Sex: 50% (14/28) male</td>
<td></td>
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</tr>
<tr>
<td>Patient selection criteria: Eastern Cooperative Oncology Group performance status ≤2, serum bilirubin ≤2.0 mg/dl, platelet count &gt;100,000, serum creatinine ≤1.5 mg/dl. Exclusion criteria included biopsy-proven cirrhosis or evidence of significant portal hypertension by history, endoscopy, or radiologic studies.</td>
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<tr>
<td>Technique: double balloon inferior vena cava catheter system (Delcath System, Delcath Inc.) was used, with melphalan. A planned treatment course included 4 treatments, each separated by 4 weeks. In the feasibility part of the study, 12 patients were treated at a dose of 2.0 mg/kg before melphalan dose escalation. Subsequent cohorts of 3 patients were enrolled at 2.5, 3.0 and 3.5 mg/kg. Four additional patients were treated at the maximum tolerated dose after a dose-limiting toxicity was confirmed in 2 of 6 patients.</td>
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<tr>
<td>Follow-up: not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conflict of interest/source of funding: none</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations used: AST, aspartate aminotransferase; GI, gastrointestinal; HCC, hepatocellular carcinoma; PIHP, percutaneous isolated hepatic perfusion

**Follow-up issues:**
- 1 patient withdrew from the study after 1 treatment and is included in the toxicity assessment only.
- All patients were followed up until disease progression with physical examination, laboratory tests, CT scan of the chest, abdomen and pelvis, and MRI of the liver every 3 months for the first year and every 4 months thereafter.

**Study design issues:**
- Phase I study.
- The purpose of the study was to demonstrate feasibility in an initial cohort and subsequently determine the maximum tolerated dose and dose-limiting toxicity of melphalan.
- Response and duration of response were scored only for lesions in the liver.

**Study population issues:**
- Most patients had received previous treatment for hepatic metastases (13 systemic chemotherapy, 7 regional chemotherapy, 4 resection, 2 radiofrequency ablation).

**Other issues:**
- Patients with evidence of disease progression on interval evaluation were not offered additional treatments. A single patient was re-enrolled on the trial after disease recrudescence following prolonged complete response (10 months).
### Study details

**Case series (prospective)**

- Japan
- Study population: patients with multiple advanced HCC (18 stage IVA and 7 stage IVB)
- n=25
- Age: mean 54.7 years; Sex: 76% (19/25) male

Patient selection criteria:
- Adequate liver function reserve for planned hepatectomy; age 10–70 years; WHO performance status ≤2 and life expectancy greater than 3 months; serum bilirubin ≤2.5 mg/dl; 15-minute indocyanine green retention rate (ICGR15) 35% or less; serum AST 300 IU/l or less; platelets 50,000/mm$^3$ or more; no pre-existing heart disease.
- No patients were candidates for surgical resection with curative intent or local ablative therapies because of the number, size or bilobar distribution of the liver tumours.

Technique: Reductive surgery was done first, followed by PIHP 1–3 months later, with doxorubicin. The time intervals between PIHP schedules ranged from 1–4 months. During hepatic arterial infusion catheter placement, the gastroduodenal artery was embolised with coils. The first 2 patients were treated by a double balloon technique but a single catheter technique was used for the remaining patients, with a specially designed 4-lumen/2-balloon catheter.

**Follow-up: median 25 months (range 3–97)**

Conflict of interest/source of funding: none reported

### Key efficacy findings

- Number of patients analysed: 22

**Tumour response:**
- Complete remission (defined as no evidence of neoplastic disease)=45.4% (10/22)
- Partial response (defined as reduction in total tumour load of more than 50%)=40.9% (9/22)
- Stable disease (defined as no change, reduction of less than 50% or increase of less than 25%)=9.1% (2/22)
- Progressive disease (defined as an increase of 25% or more)=4.5% (1/22)

The median duration of response in responders was 16 months (range 4–93).

10 patients died at 5, 9, 11, 13, 16, 18, 20, 25, 25, and 29 months after reductive surgery; 7 died of tumour progression in the liver, 2 died of respiratory failure caused by multiple lung metastases, and 1 died of massive cerebral infarction caused by tumour embolism.

**Actuarial survival rates (n=22):**
- 1-year=86%
- 5-year=47%
- 5-year survival rate for 18 stage IVA patients=57%

Survival of patients with and without cirrhosis did not differ significantly (p=0.28). Patients with and without macroscopic portal involvement had similar survival rates (p=0.76)

### Key safety findings

- Complications and toxicities after PIHP:
  - Peak serum AST level >180 IU/l=77.2% (17/22)
  - Leuokopaenia<2000/mm$^3$=45.4% (10/22)
  - Hair loss=63.6% (14/22)
  - Nausea/vomiting=13.6% (3/22)

GI toxicities including stomatitis, gastritis, and ulcers were not observed in any patients.

There was no cardiac toxicity.

### Comments

- There may be some patient overlap with Ku Y et al, 1998.

**Follow-up issues:**
- Three patients died within 4 months of reductive surgery and were not treated by PIHP.
- Patients were followed up bimonthly during the first year and every 3 months thereafter.

**Study design issues:**
- Primary endpoint was the rate of local tumour control. Secondary endpoints for efficacy were duration of response and overall survival.

**Study population issues:**
- 14 patients had chronic hepatitis and 8 patients had cirrhosis.
- 7 patients had extrahepatic metastases.
### Study details

<table>
<thead>
<tr>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour response in patients with HCC (n=28):</strong></td>
<td>During the first treatment of the hepatic vein isolation test period, 10.9% (5/46) of patients developed progressive hypotension. The test was repeated with additional fluid or inotropic agent support.</td>
<td>There may be some patient overlap with Ku Y et al, 2004</td>
</tr>
<tr>
<td>- Complete=19% (5/27)</td>
<td>2 early patients with HCC died because of complications relating to the hepatic arterial infusion catheter: 2 months after the procedure, hepatic arterial thrombosis occurred that was associated with infection caused by the catheter system implanted in the groin.</td>
<td>Follow-up issues:</td>
</tr>
<tr>
<td>- Partial=44% (12/27)</td>
<td></td>
<td>- Patients were followed up 1 month after treatment and at 1–3 month intervals thereafter.</td>
</tr>
<tr>
<td>- Stable disease=26% (7/27)</td>
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<tr>
<td>- Progressive disease=11% (3/27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(the response could not be evaluated in 1 patient who died from necrotising pancreatitis 1 month after treatment)</td>
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<tr>
<td>Four patients with complete remission were alive and disease-free at 21, 25, 28 and 43 months after the first treatment, respectively. One patient with complete remission died after 8 months from pulmonary metastases.</td>
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<tr>
<td>1-year survival rate=68%</td>
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<tr>
<td>5-year survival rate=40%</td>
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<td></td>
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<tr>
<td>Median survival of all 28 patients=16 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumour response in patients with metastatic liver cancer (n=18)</strong></td>
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</tr>
<tr>
<td>1 patient with breast cancer and 1 with malignant melanoma had a partial response. In 9 of 15 patients with colorectal metastases, liver tumours developed liquefaction after treatment; 7 of these patients had a rapid decline in serum carcinoembryonic antigen (CEA) level to below 50% of the value before treatment within 2 months. In most patients, it rose again within 3 months. In 2 patients with repeated treatments using cisplatin, low CEA levels remained for 6 months after treatment.</td>
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</tr>
</tbody>
</table>

### Abbreviations used:
- AST, aspartate aminotransferase
- GI, gastrointestinal
- HCC, hepatocellular carcinoma
- PIHP, percutaneous isolated hepatic perfusion

### Assessments

#### Case series (prospective)

**Japan**

**Recruitment period:** 1989–97

**Study population:** patients with unresectable malignant liver tumours (28 HCC, 15 colorectal metastases, 2 breast cancer metastases, 1 malignant melanoma metastasis)

**n=46**

**Age:** not reported; **Sex:** not reported

**Patient selection criteria:** no pre-existing heart disease, Karnofsky’s performance rating of 40% or more, serum bilirubin <2.5 mg/dl, 15-min indocyanine green retention rate <35%, AST <300 IU/l, platelet count >50,000/mm³, no episodes of hepatic encephalopathy, no oesophageal varices at risk for bleeding.

**Technique:** A 4-lumen/2-balloon catheter system was used. Doxorubicin was initially chosen as the first-line chemotherapeutic agent but cisplatin was used for the more recent patients. Repeat treatment was scheduled at 3–5 week intervals. The gastroduodenal and right gastric arteries were embolised with coils, whenever possible, before fixing the tip of the hepatic artery infusion catheter.

**Follow-up:** not reported

**Conflict of interest/source of funding:** not reported
### Study details

<table>
<thead>
<tr>
<th>Case series (prospective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
</tr>
<tr>
<td>Recruitment period: 1990–3</td>
</tr>
<tr>
<td>Study population: patients with primary or metastatic tumours of the liver (6 primary, 8 colorectal metastases, 2 melanoma, 4 sarcoma, 1 adrenal, 1 pancreatic and 1 small cell)</td>
</tr>
<tr>
<td>n=23</td>
</tr>
<tr>
<td>Age: median 62 years (39–74); Sex: 78% (18/23) male</td>
</tr>
<tr>
<td>Patient selection criteria: age &gt;18 years; no chemotherapy or radiotherapy within 3 weeks of enrolment, performance status ≤ Eastern Cooperative Oncology 2; serum creatinine&lt;2.0 mg/dl, white blood cell count ≥3,500/µl, absolute granulocyte count ≥1500/µl, haemoglobin≥10 g/dl, platelet count ≥100,000/µl, serum calcium &lt;12.0 mg/dl, bilirubin&lt;3.0 mg/dl, AST and alkaline phosphatase less than 5 times upper limit of normal, prothrombin time ≤150% of control; normal ECG. Exclusion criteria included other intrahepatic therapy within the last 6 months; dominant malignant disease outside the liver, significant portal hypertension, ascites, encephalopathy; recent variceal haemorrhage; allergy to heparin or venogram dye; other life-threatening illness.</td>
</tr>
<tr>
<td>Technique: double balloon inferior vena cava catheter system (Delcath System, Delcath Inc.) was used, with intravenous sedation. 12 patients received dose escalations of fluorouracil (5-FU), and 9 received dose escalations of doxorubicin.</td>
</tr>
<tr>
<td>Follow-up: not reported</td>
</tr>
</tbody>
</table>

### Key efficacy findings

- Number of patients analysed: 21
- The procedure was aborted in 2 patients because of difficulty in positioning the cephalad balloon.
- Tumour response:
  - ‘Significant response’=9.5% (2/21)
  - Both patients were treated with doxorubicin. In 1 patient, a 96% reduction of liver tumours was achieved with complete resolution of symptoms, after 4 treatment sessions. The patient was still alive 21 months after initiation of treatment. In the second patient, there was more than 50% reduction in the 2 larger lesions and several small lesions disappeared.
  - Progression of hepatic tumours=80.9% (17/21)
  - Stable disease at time of evaluation (6 or 12 weeks after procedure)=9.5% (2/21)

### Key safety findings

- There were no complications specifically related to hepatic arterial infusion such as cholecystitis or catheter-associated thrombosis of the hepatic artery. There were no treatment-related mortalities or unexpected toxicities.
- Toxicity (n=21 patients, 56 treatments):
  - Anaemia (grade 3/4)=8.9% (5/56)
  - Leukopaenia/ neutropaenia (grade 3/4)=21.4% (12/56)
  - Thrombocytopenia (grade 3/4)=1.8%
  - Nausea/vomiting=28.6% (16/56)
  - Fever=37.5% (21/56)
  - Infection=7.1% (4/56) (3 urinary tract infections treated with broad-spectrum antibiotics)
  - Cardiovascular=85.7% (48/56) (transient hypotension during balloon occlusion only, except in 4 incidents: 2 brachyarrhythmia, 1 premature ventricular contraction, 1 deep vein thrombosis)
  - Hepatic=10.7% (6/56)
  - Hair loss=12.5% (7/56)
  - Femoral vein bleed=12.5% (7/56) (all classified as minor [grade 1], caused by vomiting)

### Comments

- Follow-up issues:
  - Response to therapy was assessed every 6 weeks.
- Study design issues:
  - The objectives of the study were to demonstrate the feasibility and safety of the procedure and to identify the maximum-tolerated dose of the chemotherapeutic agents.
  - Each patient received 2 treatments at 3-week intervals. Those showing stabilisation or response received additional treatments.
- Study population issues:
  - 4 patients had extrahaemorrhagic disease.
  - 11 patients had prior chemotherapy, 1 patient had prior hormone therapy and 3 patients had prior immunotherapy.
### Study details

<table>
<thead>
<tr>
<th>FDA (2013)</th>
<th>Case series (prospective)</th>
<th>Study population: patients with unresectable primary or metastatic hepatic malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
<td>n=121 (51 phase 2, 70 phase 3)</td>
</tr>
<tr>
<td>Age: median 53 (phase 2) and 56 years (phase 3)</td>
<td></td>
<td>Patient selection criteria: phase 2 study included patients with unresectable primary or metastatic hepatic malignancies, including adenocarcinoma of the gastrointestinal tract, ocular or cutaneous melanoma, or neuroendocrine tumours (with the exception of gastrinoma). All patients were required to have minimal to no extrahepatic metastases. Phase 3 study included patients with unresectable hepatic metastases from ocular or cutaneous melanoma. Key inclusion criteria included: histological or cytological confirmation, measurable disease by CT and/or MRI, limited extrahepatic disease if the life-limiting component of disease was in the liver. Eastern Cooperative Oncology Group performance status &lt;3, adequate hepatic function, adequate haematological function. Key exclusion criteria included: Childs B or C cirrhosis or portal hypertension, congestive heart failure, previous treatment with melphalan.</td>
</tr>
<tr>
<td>Technique: The Melblez kit (Delcath Systems Inc) was used (melphalan hydrochloride and a hepatic delivery system for percutaneous hepatic perfusion, including an extracorporeal circuit with haemofiltration).</td>
<td></td>
<td>Follow-up: not reported</td>
</tr>
<tr>
<td>Conflict of interest/source of funding: manufacturer briefing document</td>
<td></td>
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</tr>
</tbody>
</table>

### Key efficacy findings

Efficacy data have not been presented because the report is not published in a peer-reviewed journal.

- Any adverse event=95.0% (115/121)
- Serious adverse event=83.5% (101/121)
- Adverse event resulting in death=4.1% (5/121) (1 ruptured right hepatic artery leading to GI haemorrhage, 1 hepatic failure [autopsy showed liver tissue was >90% tumour], 1 gastric perforation [autopsy showed 2 gastric ulcers that likely resulted from infusion of melphalan during a hepatic artery spasm with consequent misperfusion], 1 streptococcal sepsis, 1 neutropaenia)
- Adverse event leading to treatment discontinuation=38.0% (46/121)
- Neutropaenia=87% (105/121)
- Serious neutropaenia=59% (71/121)
- Complicated neutropaenia (febrile neutropaenia or neutropaenic infection)=21% (25/121)
- Thrombocytopenia=80% (97/121)
- Anaemia=59% (71/121) (approximately 56% of patients received a packed red blood cell transfusion and 18% received erythropoietin; 4 patients were discontinued from study treatment)
- Cardiovascular events=24% (29/121) (10 patients discontinued study treatment)
- Grade 3/4 cardiovascular events=17% (21/121) (13 peri-procedure, 7 post-procedure: 6 troponin increased, 2 hypotension, 3 thrombosis, 3 troponin I increased, 1 intracranial haemorrhage, 2 pulmonary embolism, 2 vena cava thrombosis, 1 pericardial effusion, 1)

### Key safety findings

- Adverse events of grade 3 or greater. Related grade 2 adverse events reported. Thus, the adverse event analyses focused on adverse events of grade 3 or greater.
- The authors note that protocol amendments were made as a result of the deaths (excluding patients with a prior Whipple procedure; requiring a liver biopsy to confirm normal liver tissue if tumour burden >50%); recommending administration of nitroglycerin in the case of hepatic artery spasm; excluding patients with active intracranial metastases or brain lesions with a propensity for rupture that likely resulted from infusion of melphalan during a hepatic artery spasm with consequent misperfusion). The authors note that protocol amendments were made as a result of the deaths (excluding patients with a prior Whipple procedure; requiring a liver biopsy to confirm normal liver tissue if tumour burden >50%); recommending administration of nitroglycerin in the case of hepatic artery spasm; excluding patients with active intracranial metastases or brain lesions with a propensity for rupture that likely resulted from infusion of melphalan during a hepatic artery spasm with consequent misperfusion).

### Follow-up issues:

- Demographic data were provided for 128 patients eligible for chemosaturation treatment. Safety data were presented for a ‘Safety Population’ (n=121, 94.5%), defined as all patients for whom a study treatment or procedure was attempted.

### Study design issues:

- Combined safety data were presented from a phase 2 (n=56) and phase 3 study (n=44 chemosaturation vs 49 best alternative care). 28 patients in the control group had hepatic disease progression and were eligible to crossover to chemosaturation treatment.
- The median number of completed cycles was 3.
- Grade 1 and 2 adverse events, with the exception of treatment-related grade 2 adverse events that occurred after hospitalisation discharge, were not required to be reported. Thus, the adverse event analyses focused on adverse events of grade 3 or greater.

### Other issues:

- The authors note that protocol amendments were made as a result of the deaths (excluding patients with a prior Whipple procedure; requiring a liver biopsy to confirm normal liver tissue if tumour burden >50%); recommending administration of nitroglycerin in the case of hepatic artery spasm; excluding patients with active intracranial metastases or brain lesions with a propensity for rupture that likely resulted from infusion of melphalan during a hepatic artery spasm with consequent misperfusion). The authors note that protocol amendments were made as a result of the deaths (excluding patients with a prior Whipple procedure; requiring a liver biopsy to confirm normal liver tissue if tumour burden >50%); recommending administration of nitroglycerin in the case of hepatic artery spasm; excluding patients with active intracranial metastases or brain lesions with a propensity for rupture that likely resulted from infusion of melphalan during a hepatic artery spasm with consequent misperfusion).
Abbreviations used: AST, aspartate aminotransferase; GI, gastrointestinal; HCC, hepatocellular carcinoma; PIHP, percutaneous isolated hepatic perfusion

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<tbody>
<tr>
<td></td>
<td></td>
<td>pupillary reflex impaired, 1 somnolence, 1 subclavian vein thrombosis, 1 subendocardial ischaemia, 1 ventricular tachycardia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GI events (including gastritis, ulceration, perforation, bleeding and gall bladder-related events)=25% (30/121) (6 patients discontinued study treatment)</td>
<td></td>
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<tr>
<td></td>
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<td>• Grade 3/4 GI events=11% (13/121)</td>
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<td></td>
<td></td>
<td>• Bleeding events=13% (16/121) (4 patients discontinued study treatment; 2 intracranial haemorrhages occurred in patients with brain metastases; 1 of these patients died.)</td>
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<td></td>
<td></td>
<td>• Grade 3/4 bleeding events=7% (8/121)</td>
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<tr>
<td></td>
<td></td>
<td>• Hepatic events=44% (53/121) (7 patients discontinued study treatment)</td>
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</tbody>
</table>

Post-marketing safety
The report also notes that 1 death has been reported out of a total of 32 patients treated with this procedure. The patient died of a spontaneous retroperitoneal haemorrhage within 24 hours of the procedure completion.

to bleed).
Efficacy

Tumour response

A case series of 28 patients with primary or metastatic liver cancer reported an overall radiographic response rate of 30% (8/27): this included 2 complete responses and 6 partial responses. In the 10 patients with metastatic ocular melanoma, 2 patients had a complete response and 3 had a partial response: duration of the 2 complete responses was 10 and 12 months, respectively. A case series of 25 patients with multiple advanced hepatocellular carcinoma (HCC) reported complete remission in 45% (10/22) of patients, partial response in 41% (9/22), stable disease in 9% (2/22) and progressive disease in 5% (1/22) of patients. The median duration of response in responders was 16 months (range 4–93). A case series of 46 patients reported tumour response for 28 patients with HCC: 19% (5/27) of patients had a complete response, 44% (12/27) had a partial response, 26% (7/27) had stable disease and 11% (3/27) had progressive disease. In the same case series, there were 18 patients with metastatic liver cancer, 2 of whom had a partial response (1 with breast cancer and 1 with malignant melanoma). In 60% (9/15) of patients with colorectal metastases, liver tumours developed liquefaction after treatment; 7 of these patients had a rapid decline in serum carcinoembryonic antigen (CEA) level to below 50% of the value before treatment within 2 months but it rose again within 3 months in most patients. A case series of 23 patients with primary or metastatic liver cancer reported a ‘significant response’ in 10% (2/21) of patients, stable disease in 10% (2/21) and progression of hepatic tumours in 81% (17/21) of patients.

Overall survival

The case series of 25 patients with multiple advanced HCC reported 1-year and 5-year survival rates of 86% and 47% respectively (n=22). The case series of 46 patients reported 1-year and 5-year survival rates of 68% and 40% respectively for all 28 patients with HCC. Median survival for all 28 patients was 16 months.

Safety

Death

An adverse event resulting in death was reported in 4% (5/121) of patients in a case series of 121 patients. The causes of death were gastrointestinal haemorrhage due to a ruptured right hepatic artery, hepatic failure in a patient whose liver tissue was >90% tumour, gastric perforation, streptococcal sepsis and neutropaenia. Death was reported in 2 patients in the case series of 46 patients: 2 months after the procedure, hepatic arterial thrombosis occurred that was associated with infection caused by the catheter system.
Death was reported in 1 patient out of a total of 32 patients treated with this procedure in post-marketing surveillance. The patient died of a spontaneous retroperitoneal haemorrhage within 24 hours of the procedure completion.

**Haematological adverse events**

Serious neutropaenia was reported in 59% (71/121) of patients in the case series of 121 patients. Complicated neutropaenia (febrile neutropaenia or neutropaenic infection) was reported in 21% (25/121) of patients and was the underlying cause of death in 2 patients (described previously). Thrombocytopenia was reported in 80% (97/121) of patients. Anaemia was reported in 59% (71/121) of patients: approximately 56% of patients received a packed red blood cell transfusion and 18% received erythropoietin.

**Cardiovascular events**

Cardiovascular events classified as grade 3 or 4 were reported in 17% (21/121) of patients in the case series of 121 patients; 13 of these occurred at the time of the procedure and 7 occurred after the procedure. These included troponin increase (n=6), hypotension (n=2), troponin I increase (n=3), intracranial haemorrhage (n=1), pulmonary embolism (n=2), vena cava thrombosis (n=2), pericardial effusion (n=1), impaired pupillary reflex (n=1), somnolence (n=1), subclavian vein thrombosis (n=1), subendocardial ischaemia (n=1), and ventricular tachycardia (n=1).

**Gastrointestinal events**

Gastrointestinal events (including gastritis, ulceration, perforation, bleeding and gall-bladder related events) classified as grade 3 or 4 were reported in 11% (13/121) of patients in the case series of 121 patients.

**Haemorrhage**

Haemorrhage occurred in 13% (16/121) of patients, of which 7% (8/121) were classified as grade 3 or 4, in the case series of 121 patients. Two intracranial haemorrhages occurred in patients with brain metastases; 1 of these patients died.

**Hepatic events**

Hepatic events were reported in 44% (53/121) of patients in the case series of 121 patients; 7 patients discontinued study treatment. Hepatic failure was the cause of death in 1 patient (described previously).
Validity and generalisability of the studies

- A randomised controlled trial has been completed but the results have not yet been published in a peer-reviewed journal. A conference abstract was published in 2010 but this only includes efficacy data. According to the IP Methods Guide, conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview. Safety data from patients included in a randomised controlled trial are reported in the manufacturer’s briefing report submitted to the FDA.
- Most of the data come from small case series.
- One case series only includes patients with advanced hepatocellular carcinoma. The remaining studies include patients with either primary or metastatic liver tumours. The efficacy is likely to vary according to the type of tumour.
- Different chemotherapeutic agents are used and at different doses. This is likely to have an effect on both the safety and efficacy profile.
- In one case series, patients were treated by reductive surgery 1–3 months before chemosaturation.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures


Specialist advisers’ opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Dr R Jackson (British Society of Interventional Radiology), Mr H Malik (BASO ~ The Association for Cancer Surgery), Mr S Fenwick (Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland)

- All the specialist advisers consider the procedure to be definitely novel and of uncertain safety and efficacy.
- In the case of ocular melanoma liver metastases, there is no standard practice other than best supportive care. For other tumour types comparators would include systemic chemotherapy, TACE, and SIRT.
- Anecdotal adverse events include hepatotoxicity; haemodynamic instability during procedure; bleeding; death from unexpected disseminated intravascular coagulation. Deaths have been reported in the literature.
- Key efficacy outcomes are improvement in progression-free and overall survival, and time to progression.
• There are uncertainties about the efficacy of the procedure because numbers of patients treated are small.
• One adviser noted that as this technique is relatively novel, the whole team involved (including surgeon, IR, anaesthetist, perfusionist, critical care) should receive formal training, including visiting an established unit.
• Two specialist advisers considered the potential impact of the procedure on the NHS to be minor; one considered the potential impact to be moderate.

**Patient commentators’ opinions**

NICE’s Public Involvement Programme sent 3 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 3 completed questionnaires.

*Section to be inserted if patient commentators raised no new issues*

The patient commentators’ views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

*Section to be inserted if patient commentators raised new issues*

The patient commentators raised the following issues about the safety/efficacy of the procedure which did not feature in the published evidence or the opinions of specialist advisers, and which the Committee considered to be particularly relevant:

• [insert additional efficacy and safety issues raised by patient commentators and highlighted by IPAC, add extra rows as necessary].
• [Last item in list].

**Issues for consideration by IPAC**

• Ongoing trials:
- Hepatic Arterial Infusion of Melphalan With Hepatic Perfusion in Treating Patients With Unresectable Liver Cancer (NCT00096083). A Phase II study of hepatic arterial infusion of Melphalan with venous filtration via peripheral hepatic perfusion (PHP) for unresectable primary and metastatic cancers of the liver (USA). Estimated enrolment=105; study completion date=August 2014.

- Hepatic Arterial Infusion With Melphalan Compared With Standard Therapy in Treating Patients With Unresectable Liver Metastases Due to Melanoma (NCT00324727). A random-assignment study of hepatic arterial infusion of Melphalan with venous filtration via peripheral hepatic perfusion (PHP) (Delcath system) versus best alternative care for ocular and cutaneous melanoma metastatic to the liver (USA). Estimated enrolment=100; study completion date=not stated (study start date=February 2006).
References


Appendix A: Additional papers on chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

The following table outlines the studies that are considered potentially relevant to the 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.

<table>
<thead>
<tr>
<th>Article</th>
<th>Number of patients/follow-up</th>
<th>Direction of conclusions</th>
<th>Reasons for non-inclusion in table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behestri MV, Denny DF, Glickman MG et al. (1992) Percutaneous isolated liver perfusion for treatment of hepatic malignancy: preliminary report. Journal of Vascular and Interventional Radiology 3: 453–8</td>
<td>Case series n=8</td>
<td>Phase I dose-escalation study. 2000 mg/m² of 5-FU could be administered safely, up to 85% of the drug was removed and patients were protected from systemic toxicity.</td>
<td>A larger study from the same study centre is included (Ravikumar et al, 1994)</td>
</tr>
<tr>
<td>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</td>
<td>Case series n=10</td>
<td>Peak systemic doxorubicin levels were an average 86% lower than were peak prefiler levels (p&lt;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.</td>
<td>Small case series</td>
</tr>
<tr>
<td>Deneve JL, Choi J, Gonzalez RJ et al. (2012) Chemosaturation with percutaneous hepatic perfusion for unresectable isolated hepatic metastases from sarcoma. Cardiovascular &amp; Interventional Radiology 35: 1480-1487</td>
<td>Case report n=1</td>
<td>A total of 4 procedures were performed, with a 25% reduction in size of the largest lesion observed and 16month hepatic progression-free survival. Toxicity was mild (neutropenia) and manageable on an outpatient basis.</td>
<td>Case report.</td>
</tr>
<tr>
<td>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</td>
<td>Case series n=18 (12 evaluable for disease response)</td>
<td>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 nonresponders it was 8 months.</td>
<td>Small case series.</td>
</tr>
</tbody>
</table>
### Article Details

<table>
<thead>
<tr>
<th>Article</th>
<th>Number of patients/ follow-up</th>
<th>Direction of conclusions</th>
<th>Reasons for non-inclusion in table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ku Y, Iwasaki T, Fukumoto T et al. (1998) Induction of Long-Term Remission in Advanced Hepatocellular Carcinoma With Percutaneous Isolated Liver Chemoperfusion. Annals of Surgery 227: 519–26</td>
<td>Case series n=28</td>
<td>Duration of response in responders (complete and partial) with repeated treatments was significantly longer than that with a single treatment ($p = 0.01$). The overall survival rate by the Kaplan-Meier method was 39.7% at 5 years. The treatments were well-tolerated, and the primary side effects were mild to moderate chemical hepatitis and reversible myelosuppression.</td>
<td>A similar study from the same centre is included (Ku Y et al, 1998)</td>
</tr>
<tr>
<td>Ku Y, Tominaga M, Iwasaki T et al. (1998) Efficacy of repeated percutaneous isolated liver chemoperfusion in local control of unresectable hepatocellular carcinoma. Hepato-Gastroenterology 45: 1961-1965</td>
<td>Case series n=30 (21 evaluable)</td>
<td>Eleven (52%) of 21 evaluable patients in the single treatment group and 7 out of 8 patients (88%) in the repeated treatment group had partial or complete response. Median durations of response in responding patients were 6 and 21 months in the single and the repeated groups, respectively ($p=0.02$). The 1- and 2-year survival rates (single vs. repeated) were 57% vs 88%, and 29% vs 70%, respectively ($p=0.05$)</td>
<td>A more recent study from the same centre is included (Ku Y et al, 2004)</td>
</tr>
<tr>
<td>Ku Y, Tominaga M, Iwasaki T et al. (1996) Percutaneous hepatic venous isolation and extracorporeal charcoal hemoperfusion for high-dose intraarterial chemotherapy in patients with colorectal hepatic metastases. Surgery Today 26 (5) 305-313</td>
<td>Case series n=12</td>
<td>Tumor liquefaction accompanied by a sharp decrease in serum carcinoembryonic antigen levels by more than 50% of pretreatment levels was observed in 6 of the 12 patients 1 month after treatment. Apart from chemical hepatitis, which developed in 11 (92%) of the patients, the Adriamycin toxicities were well controlled following the development of nausea and vomiting in 2 patients (17%), leukopenia &lt; 2,000/mm$^3$ in 3 (25%), and gastric ulcer in 1 (8%).</td>
<td>A more recent study from the same centre is included (Ku Y et al, 2004)</td>
</tr>
<tr>
<td>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</td>
<td>Case series n=51</td>
<td>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 favor administration of general anesthesia, rather than sedation, for patients undergoing PHP</td>
<td>The study focuses on anaesthetic, haemodynamic and metabolic aspects of the procedure.</td>
</tr>
<tr>
<td>Article</td>
<td>Number of patients/ follow-up</td>
<td>Direction of conclusions</td>
<td>Reasons for non-inclusion in table 2</td>
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</table>
• 3 severe neutropaenia  
One partial response was observed.                                                                                                                                                        | Small case series – technique did not include extracorporeal haemofiltration.                        |
| Suzuki Y, Ku Y, Tominaga M et al. (2000) Two-staged treatment with local resection and percutaneous isolated hepatic chemoperfusion for advanced pancreatic cancer with multiple liver metastases: report of a case. Hepato-Gastroenterology 48: 574–7 | Case report n=1             | The second percutaneous isolated hepatic perfusion with high-dose cisplatin and mitomycin G demonstrated a distinct regression of metastatic liver tumors. Although a long-term patient survival was not obtained due to local recurrence, liver metastases were well controlled. | Case report.                                                                                         |
| Van Etten B, Brunstein F, van Ijken MG et al. (2004) Isolated hypoxic hepatic perfusion with orthograde or retrograde flow in patients with irresectable liver metastases using percutaneous balloon catheter techniques: a phase I and II study. Annals of Surgical Oncology 11: 598–605 | Case series n=18            | Although local drug concentrations were high with retrograde IHHP, systemic toxicity was still moderate to severe. Partial responses were seen in 12% and stable disease in 81% of patients. The median time to local progression was 4.8 months. | Small case series - technique did not include extracorporeal haemofiltration.                       |
Appendix B: Related NICE guidance for chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

<table>
<thead>
<tr>
<th>Guidance</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions procedures</td>
<td><strong>Selective internal radiation therapy for primary hepatocellular carcinoma. NICE interventional procedure guidance 460 (2013).</strong></td>
</tr>
<tr>
<td></td>
<td>1.1 Current evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and audit. Uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment.</td>
</tr>
<tr>
<td></td>
<td>1.2 Patients with primary hepatocellular carcinoma should be selected for treatment by SIRT or for entry into trials by a multidisciplinary hepatobiliary cancer team.</td>
</tr>
<tr>
<td></td>
<td>1.3 SIRT should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of side effects from the procedure.</td>
</tr>
<tr>
<td></td>
<td>1.4 Clinicians should enter details about all patients undergoing SIRT for primary hepatocellular carcinoma onto the UK SIRT register. They should audit and review clinical outcomes locally and should document them and consider their relationship to patient characteristics.</td>
</tr>
<tr>
<td></td>
<td><strong>Selective internal radiation therapy for primary cholangiocarcinoma. NICE interventional procedure guidance 459 (2013).</strong></td>
</tr>
<tr>
<td></td>
<td>1.1 Current evidence on the safety and efficacy of selective internal radiation therapy (SIRT) for primary intrahepatic cholangiocarcinoma is limited in both quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.</td>
</tr>
<tr>
<td></td>
<td>1.2 Clinicians wishing to undertake SIRT for primary intrahepatic cholangiocarcinoma should take the following actions.</td>
</tr>
<tr>
<td></td>
<td>• Inform the clinical governance leads in their Trusts.</td>
</tr>
<tr>
<td></td>
<td>• Ensure that patients understand the uncertainty about the procedure's safety and efficacy, and</td>
</tr>
</tbody>
</table>
provide them with clear written information. In addition, the use of NICE’s information for the public is recommended.

1.3 Patients with primary intrahepatic cholangiocarcinoma should be selected for treatment by SIRT or for entry into trials by a multidisciplinary hepatobiliary cancer team.

1.4 SIRT should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of side effects from the procedure.

1.5 Clinicians should enter details about all patients undergoing SIRT for primary intrahepatic cholangiocarcinoma onto the UK SIRT register. They should audit and review clinical outcomes locally and should document them and consider their relationship to patient characteristics.

1.6 NICE encourages research to guide future use of SIRT for primary intrahepatic cholangiocarcinoma. This should document patient characteristics, tumour response, survival and quality of life measures, and details of other treatments used adjunctively or sequentially. NICE may review the procedure on publication of further evidence.

**Microwave ablation for the treatment of metastases in the liver. NICE interventional procedure guidance 406 (2011).**

1.1 Current evidence on microwave ablation for the treatment of liver metastases raises no major safety concerns. The evidence on efficacy is inadequate in quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to undertake microwave ablation for the treatment of liver metastases should take the following actions.

- Inform the clinical governance leads in their Trusts.
- Ensure that patients and their carers understand the uncertainty about the procedure’s efficacy and provide them with clear written information, including details about other treatment options. In addition, use of NICE’s information for patients (‘Understanding NICE guidance’) is recommended (available from www.nice.org.uk/guidance/IPG406/publicinfo).
- Audit and review clinical outcomes of all patients having microwave ablation for the treatment of liver metastases (see section 3.1).

1.3 Patient selection should be carried out by a hepatobiliary cancer multidisciplinary team.

1.4 NICE encourages further research into microwave ablation for the treatment of liver metastases. Research should clearly define patient selection criteria and report
tumour recurrence and patient survival. Comparison with other ablative techniques would be useful. NICE may review the procedure on publication of further evidence.

**Cryotherapy for the treatment of liver metastases. NICE interventional procedure guidance 369 (2010).**

1.1 Current evidence on the safety of cryotherapy for the treatment of liver metastases appears adequate in the context of treating patients whose condition has such a poor prognosis, but the evidence on efficacy is inadequate in quality. Therefore cryotherapy for the treatment of liver metastases should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to undertake cryotherapy for the treatment of liver metastases should take the following actions.

- Inform the clinical governance leads in their Trusts.
- Ensure that patients and their carers understand that other ablative treatments are available and provide them with clear written information. In addition, the use of NICE’s information for patients ('Understanding NICE guidance') is recommended.
- Audit and review clinical outcomes of all patients having cryotherapy for liver metastases (see section 3.1).

1.3 Patient selection and treatment should be carried out by a hepatobiliary multidisciplinary team with expertise in the use of ablative techniques.

**Microwave ablation of hepatocellular carcinoma. NICE interventional procedure guidance 214 (2007).**

1.1 Current evidence on the safety and efficacy of microwave ablation of hepatocellular carcinoma appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.

1.2 Patient selection should be carried out by a multidisciplinary team that includes a hepatobiliary surgeon.

1.3 The procedure should be performed under appropriate imaging guidance.

1.4 A number of devices are available, and there is some uncertainty about the energy levels that should be used. Any adverse events relating to this procedure should be reported to the Medicines and Healthcare products Regulatory Agency.

1.5 Further research on long-term survival outcomes and comparisons of microwave ablation with other ablative techniques will be useful.
Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007).
1.1 Limited evidence on the safety and efficacy of radiofrequency (RF)-assisted liver resection appears adequate to support the use of this procedure as one of the options for liver resection, provided that the normal arrangements are in place for consent, audit and clinical governance.

1.1 Current evidence on the efficacy of living-donor liver transplantation and its safety profile appears adequate to support the use of this procedure for suitable recipients.
1.2 However, current evidence suggests that living-donor liver transplantation carries a significant risk of morbidity and a small risk of death for donors. Therefore clinicians wishing to undertake this procedure should take the following actions.
  - Inform the clinical governance leads in their Trusts.
  - Ensure that donors and recipients undergo thorough physical and psychological screening, and receive counselling about the morbidity and risks associated with this procedure. They should also be provided with clear written information. In addition, use of the Institute’s information for patients is recommended.
  - Audit and review clinical outcomes of all people donating liver tissue for transplantation (see section 3.1).
1.3 Living-donor liver transplantation should only be performed on patients selected using UK Transplant Liver Advisory Group standards in specialist centres and in the context of a multidisciplinary team.
1.4 Clinicians should enter all donors and recipients into the UK & Ireland Liver Transplant Audit.

1.1 Current evidence on the safety and efficacy of laparoscopic liver resection appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance.
1.2 Patient selection for laparoscopic liver resection should be carried out by a multidisciplinary team. Surgeons undertaking laparoscopic liver resection should have specialist training and expertise both in laparoscopic techniques and in the specific issues relating to liver surgery.
Radiofrequency ablation of hepatocellular carcinoma.  

1.1 Current evidence of the safety and efficacy of radiofrequency ablation (RFA) for hepatocellular carcinoma appears adequate to support use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.

1.2 It is recommended that:
- patient selection should be carried out by a multidisciplinary team that includes a hepatobiliary surgeon
- the procedure should be monitored by CT or ultrasound.
Appendix C: Literature search for chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

<table>
<thead>
<tr>
<th>Database</th>
<th>Date searched</th>
<th>Version/files</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)</td>
<td>26/09/2013</td>
<td>Issue 9 of 12, September 2013</td>
</tr>
<tr>
<td>Database of Abstracts of Reviews of Effects – DARE (CRD website)</td>
<td>26/09/2013</td>
<td>Issue 3 of 4, July 2013</td>
</tr>
<tr>
<td>HTA database (CRD website)</td>
<td>26/09/2013</td>
<td>Issue 3 of 4, July 2013</td>
</tr>
<tr>
<td>Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)</td>
<td>26/09/2013</td>
<td>Issue 8 of 12, August 2013</td>
</tr>
<tr>
<td>MEDLINE (Ovid)</td>
<td>26/09/2013</td>
<td>1946 to September Week 3 2013</td>
</tr>
<tr>
<td>MEDLINE In-Process (Ovid)</td>
<td>26/09/2013</td>
<td>September 25, 2011</td>
</tr>
<tr>
<td>EMBASE (Ovid)</td>
<td>26/09/2013</td>
<td>1974 to 2013 Week 38</td>
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<tr>
<td>PubMed</td>
<td>27/09/2013</td>
<td>n/a</td>
</tr>
<tr>
<td>BLIC (Dialog DataStar)</td>
<td>27/09/2013</td>
<td>n/a</td>
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</tbody>
</table>

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

1 Liver Neoplasms/

2 ((liver or hepatic* or hepatocell*) adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metastas*)).tw.

3 (hepatoma* or cholangiocarcinoma* or hepatocarcinoma* or HCC).tw.

4 1 or 2 or 3

5 Chemotherapy, Cancer, Regional Perfusion/

6 ((Percut* or isolate*) adj3 (hepat* or liver*) adj3 (perfus* or chemoperfus*)).tw.

7 CS-PHP.tw.

8 PHP.tw.

IP overview: Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

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**IP overview:** Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer of the liver

<p>| | |</p>
<table>
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<tr>
<td>12</td>
<td>Delcath.tw.</td>
</tr>
<tr>
<td>13</td>
<td>((Hepat* or liver*) adj3 (vein* or venous* or arter* or outflow*) adj3 (isolat* or segregate*)).tw.</td>
</tr>
<tr>
<td>14</td>
<td>5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13</td>
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<tr>
<td>15</td>
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</tr>
<tr>
<td>16</td>
<td>animals/ not humans/</td>
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<tr>
<td>17</td>
<td>15 not 16</td>
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