Hepatic Perfusion Therapy

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**KEYWORDS**
- Isolated hepatic perfusion
- Hepatocellular carcinoma
- Melanoma
- Colorectal cancer
- Hepatic metastases
- Regional therapies
- Percutaneous hepatic perfusion

**KEY POINTS**
- Isolated hepatic perfusion (IHP) depends on the unique vascular structure of the liver to deliver cytotoxic chemotherapies to liver malignancies. Cytotoxic chemotherapy is delivered via the hepatic artery and extracted from the retrohepatic inferior vena cava to reduce systemic leakage.
- Hepatic perfusion has been used with oncologic efficacy in patients with metastatic ocular melanoma, hepatocellular carcinoma, and colorectal cancer liver metastases, among other histologies.
- Advances in techniques of chemosaturation with percutaneous hepatic perfusion may offer novel minimally invasive avenues of treating patients with metastatic disease.

**INTRODUCTION**

Although curative surgical resection is the optimal treatment of primary and metastatic malignancies of the liver, few patients are eligible because of the unique biology of liver disease. Regional therapies of the liver use the hepatic arterial-dominant supply of tumors to deliver high concentrations of chemotherapy, embolic particles, and radiation. Perfusion, as opposed to infusion, relies on the flow of cytotoxic therapy through the liver with extraction of the drug via the venous outflow. The anatomic reliance on the vascular supply of the liver is paramount in the ability to perform an isolated hepatic perfusion.

**SURGICAL TECHNIQUE AND SELECTION OF PATIENTS**

Hepatic perfusion has been performed for numerous histologic subtypes, but the largest body of evidence exists for its use in patients with metastatic ocular melanoma.

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melanoma, colorectal liver metastases, neuroendocrine tumors, and primary liver tumors including hepatocellular carcinoma and cholangiocarcinoma. There are three broad methods of performing a hepatic perfusion: (1) isolated hepatic perfusion (IHP), (2) percutaneous hepatic perfusion (PHP; a misnomer because it indicates chemosaturation), and (3) liver perfusional chemotherapy (which is primarily infusional).

**Selection of Patients**

Before a liver perfusion, it is important to consider a few additional factors related to general oncologic surgical principles. Hepatic arterial anatomy can vary at least 20% of the time with the commonest anatomic variations shown in Fig. 1.

Although hepatic perfusion can be considered in patients with variants in anatomy, it is important to understand the hepatic arterial anatomy in great detail before attempting a perfusion. In addition, it is critically important to select patients who are robust enough to undergo the procedure and can tolerate any complications. Because up to 22% of patients can develop veno-occlusive disease and a few patients develop vanishing bile duct syndrome (more commonly seen with hepatic artery infusion [HAI] pumps), it is important to select patients with intact synthetic and excretory function of the liver. Although pretreatment with chemotherapy is not a contraindication

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**Fig. 1.** Michels classification of hepatic arterial anatomy. A. LHA, accessory left hepatic artery; A. RHA, accessory right hepatic artery; CA, celiac artery; CHA, common hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery; LHA, left hepatic artery; PHA, proper hepatic artery; R. LHA, replaced left hepatic artery; R. RHA, replaced right hepatic artery; RHA, right hepatic artery; SA, splenic artery; SMA, superior mesenteric artery. (From Caserta MP, Sakala M, Shen P, et al. Presurgical planning for hepatobiliary malignancies: clinical and imaging considerations. Magn Reson Imaging Clin N Am 2014;22(3):447–65; with permission.)
to the procedure, it is important to note hematologic parameters of patients before planning the procedure.

**Technical Details of an Isolated Hepatic Perfusion**

Modern techniques of hepatic perfusion have significantly advanced since its original advent by Ausman and subsequent refinement by Skibba and Quebbeman at the Medical College of Wisconsin. A hybrid technique of an IHP has been adopted by many centers, which combines advances in percutaneous and open surgery. Anesthetic considerations for an IHP include the ability to place the patient on venovenous bypass, and need for systemic heparinization during the case. An epidural is generally discouraged because of the risk of an epidural hematoma, and preoperative assessment of neck and femoral veins is often undertaken to ensure successful placement of the cannulas. Fluid management is essential to ensure easy mobilization of the liver, but extreme fluid restriction is not necessary as needed in hepatic resection.

The procedure often begins with the placement of a 17F to 19F catheter cannula in the right internal jugular vein and an 8F catheter central venous line in the left internal jugular vein for access (Video 1). A diagnostic laparoscopy is undertaken to rule out extrahepatic disease. Wide exposure is gained by a right subcostal incision with a midline extension. A cholecystectomy is not always necessary but routinely performed to reduce the risk of cholecystitis. Complete mobilization of the liver and the inferior vena cava (IVC) are essential for this procedure. The right adrenal vein is usually ligated and divided, and occasionally the phrenic veins also need to be dissected and divided. Control of the infrahepatic IVC is gained by encircling it with a Rummel tourniquet and the suprahepatic IVC is controlled with the angled vascular clamp. The portal dissection includes dissecting at least 2 cm of the gastroduodenal artery (GDA) and identifying the common hepatic artery to clamp it. The portal triad is not completely dissected and an angled clamp is chosen to create complete portal occlusion. Wires are then placed through bilateral femoral vein access into the IVC and systemic heparinization is reached with a target activated clotting time greater than 300. At this point, a 17F to 19F catheter is placed via the left femoral vein and is positioned by palpation of the distal IVC/common iliac vein. A 14F catheter cannula is also threaded through the right femoral vein and is placed in the retrohepatic IVC. The Rummel tourniquet is clamped around the retrohepatic cannula and the venovenous bypass circuit is begun from the left femoral vein access to the internal jugular access (Fig. 2). At this point, the GDA is cannulated with a 5F catheter cannula and the proximal common hepatic artery is clamped. The porta hepatis is also clamped, as is the suprahepatic IVC, and an oxygenated pH balanced perfusion is begun through the GDA into the liver with a retrohepatic drainage. Flow rates of 400 to 700 mL/min are achieved and the inline arterial pressures are kept less than 150 mm Hg. Temperature probes are used to monitor the temperature of the liver, which is increased to 40°C. The perfusate leakage can often be detected by stability of the reservoir volume. Although historically perfusate leakage was documented using radiolabelled tracers, this method seems to be quite effective without adding extra logistic steps. The reservoir volume can fluctuate minimally because of expansion of the liver or leakage from the capsule but this should be completely stable before adding the chemotherapy drug. Cytotoxic chemotherapy (usually melphalan) is added and constant adjustment of the milieu is necessary to maintain a pH of 7.20 during the perfusion. Following a 60-minute perfusion, washout of the liver with crystalloid, and colloid and replacement of plasma with fresh frozen plasma occurs. Decannulation of the hepatic perfusion occurs, with either ligation of the GDA or subsequent preparation of the artery for placement of HAI pump. The venovenous circuit is decannulated and the heparinization is reversed. Some
techniques with variant arterial anatomy described by some authors are shown in Fig. 3.

Special attention should be paid to massive hepatocyte injury, loss of synthetic function, and hematologic derangements during perioperative recovery. Occurrence of veno-occlusive disease and disappearing bile ducts are subacute toxicities of the perfusion. Experienced critical care staff is necessary during the early postoperative period of the patient’s care.

**Variants of the Perfusion**

1. Choice of venovenous circuit access: As with cardiac surgery, venovenous access is easily obtained via the axillary vein, the saphenous vein, or other similar venous access structures.

2. Orthograde versus retrograde portal flow: Current techniques use portal occlusion, which leads to orthograde flow. This has been shown to have up to a 55% leakage of perfusate in some studies. Retrograde flow has been proposed to reverse the

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portal flow and allow the portal vein to drain the blood from the liver. Leakage occurs with both techniques.

3. Hypoxic perfusion: Some authors have suggested the use of hypoxia to augment the cytotoxic effects of the drug. The rate of severe systemic toxicity of hypoxic perfusions is 0% to 4% and the outcomes in two papers are similar to reported outcomes of classical IHP.

4. Tumor necrosis factor (TNF)-α in the perfusion: The use of immunomodulating drugs, such as TNF, has been proposed in early studies of the IHP. Early results, although promising, have not been substantiated, and toxicity remains high.

Percutaneous Hepatic Perfusion (Chemosaturation)

PHP achieves vascular isolation and chemosaturation with cytotoxic chemotherapy. Unlike the normal IHP circuit where cytotoxic chemotherapy is extracted before leakage or absorption into the circulation, the PHP circuit relies on extracorporeal hemofiltration to remove the chemotherapy (Fig. 4). This leads to two unintended consequences (delivering higher concentrations of drug with a shorter duration, and filtration of catecholamines), leading to profound hemodynamic alterations. Regardless, this is a minimally invasive procedure that can be repeated with minimal risk to the patient. Contrast allergy is a relative contraindication for this procedure, although CO2 angiography and premedication could be used as an alternative. The procedure uses the Delcath catheter to create isolation of the hepatic venous outflow (Delcath Systems, Inc, New York, NY). A balloon is usually inflated to 20 to 35 mL after systemic heparinization and is used to snag the cavoatrial junction under fluoroscopy. The distal IVC balloon is used to flatten out the IVC in a suprarenal position and confirmation of vascular isolation is achieved by a contrast venogram. The hepatic artery is cannulated percutaneously. Occasionally, the GDA is coil embolized to reduce leakage via the artery. Nitroglycerin and papaverine are often used to reduce vasospasm. Chemosaturation then occurs for 30 minutes during which significant hemodynamic support is required because of catecholamine losses. Although veno-occlusive disease and vanishing bile duct syndrome can occur, the commonest toxicity is hematologic. The usual hospital length of stay is 3 to 5 days after such a procedure.

LIVER PERFUSIONAL CHEMOTHERAPY

The technique of liver perfusional chemotherapy has been popularized in Japan, and although termed perfusional chemotherapy, this is best classified as an infusional chemotherapy. This technique uses two catheters placed at the time of surgery into the hepatic artery and the portal vein (via the middle colic vein) through which chemotherapy is administered for 28 days after resection. This has been used in the adjuvant/prophylactic setting with demonstrable feasibility, although oncologic durability is unknown. Regardless, the lack of extraction of chemotherapy other than by bioavailability makes this more of an infusion akin to hepatic arterial infusional therapies.

OCULAR MELANOMA

Metastatic ocular melanoma has poor overall survival and liver metastases are no exception. Trials of MAP-kinase inhibitors against standard dacarbazine/temozolomide chemotherapy have shown improved progression-free survival (15.9 vs 7 weeks) and objective response rates (14% vs 0%). Despite advances in
anti-BRAF therapy, such as vemurafenib, the utility is limited for patients with ocular melanoma metastases who do not harbor such mutations.\textsuperscript{18} Immunotherapy trials including checkpoint inhibitors do not usually include patients with ocular melanoma, and such drugs as selumetinib have shown only marginal benefit.\textsuperscript{17,19} IHP has been shown to have significant survival benefit in patients with ocular melanoma (Table 1). However, PHP has been tested in a phase III trial against the best available care, which suggested an improvement in disease-free survival. Unfortunately, the data were not published because of concerns regarding data management during the trial.\textsuperscript{20} An ongoing trial (SCANDIUM) is currently investigating the role of IHP in the management of metastatic ocular melanoma. The trial is a phase III randomized controlled trial with an expected accrual of 78 patients.\textsuperscript{21}

**HEPATOCELLULAR CARCINOMA**

Although curative resection offers 5-year overall survival rates of 40%, only 10% to 30% of patients are potential resection candidates because hepatocellular carcinoma commonly develops in the backdrop of chronic liver disease, diminishing the salvageable functional liver reserve.\textsuperscript{22,23} Feldman and colleagues\textsuperscript{24} investigated the efficacy of hyperthermic ILP using mephalan with or without TNF on primary hepatic malignancies (hepatocellular carcinoma and intrahepatic cholangiocarcinoma). Patients had advanced disease (average of 13 hepatic lesions per patient with a mean lesion size of 10 cm) and four out of nine patients had failed prior therapy. Partial radiographic response was observed in 67% of patients and toxicities were self-limited (Table 2). After promising results on an initial prospective study of reductive surgery followed by percutaneous IHP, Fukumoto and colleagues\textsuperscript{25} reported results of the same treatment in more aggressive hepatocellular carcinoma (portal vein invasion, median tumor size of 8.3 cm, BCLC stage B or C) with background liver dysfunction (cirrhosis in 33.8%, chronic hepatitis in 60.3%) and achieved an objective response rate of 70.6% and median overall survival of 25 months.

**LIVER METASTASES FROM COLORECTAL CANCER**

Studies have shown that IHP in combination with systemic or hepatic arterial chemotherapy improves response rates and overall survival in patients with colorectal liver metastases (Table 3). Melphalan alone or in combination with TNF was the most commonly used drug, although recent trials have used oxaliplatin after favorable toxicity profiles in HAI trials.\textsuperscript{26} Alexander and colleagues\textsuperscript{27} looked at the use of IHP as a second-line therapy in patients who failed first-line chemotherapy with irinotecan, and the response rate was 60% with a median survival of 12 months.
of 12 months. The role of IHP in the setting of evolving chemotherapy is still undefined. Sequencing of treatment of patients with unresectable metastatic disease with systemic chemotherapy could include liver perfusion after 2 to 3 months of systemic therapy with concurrent flouxuridine and oxaliplatin in the postoperative setting. Alternatively, liver perfusion can be used in a salvage setting after completing first-line therapy.

### Table 1

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>IHP Agent</th>
<th>ORR</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander et al,10 2000</td>
<td>22</td>
<td>Melphalan with or without TNF</td>
<td>62%</td>
<td>11</td>
</tr>
<tr>
<td>Noter et al,28 2004</td>
<td>8</td>
<td>Melphalan with or without TNF</td>
<td>50%</td>
<td>9.9</td>
</tr>
<tr>
<td>Rizell et al,29 2008</td>
<td>27</td>
<td>Melphalan</td>
<td>70%</td>
<td>7.5</td>
</tr>
<tr>
<td>van Etten et al,7 2009</td>
<td>8</td>
<td>Melphalan (hypoxic IHP)</td>
<td>37%</td>
<td>11</td>
</tr>
<tr>
<td>Varghese et al,30 2010</td>
<td>17</td>
<td>Melphalan</td>
<td>50%</td>
<td>11.6</td>
</tr>
<tr>
<td>Pingpank et al,20 2010</td>
<td>93</td>
<td>Melphalan (percutaneous IHP)</td>
<td>34%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Olofsson et al,31 2014</td>
<td>34</td>
<td>Melphalan</td>
<td>68%</td>
<td>24</td>
</tr>
<tr>
<td>Forster et al,32 2014</td>
<td>10</td>
<td>Melphalan (percutaneous IHP)</td>
<td>50%</td>
<td>12.6</td>
</tr>
</tbody>
</table>

**Abbreviations:** ORR, objective response rate; OS, overall survival.

*Data from Refs. 7,10,20,28–32*
### Table 2
Selected studies of isolated hepatic perfusion in primary hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Patients</th>
<th>Cirrhosis</th>
<th>Treatment Received</th>
<th>ORR</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukumoto et al, 2014</td>
<td>68</td>
<td>Multiple bilobar HCC</td>
<td>33.8%</td>
<td>Reductive hepatectomy + sequential PIHP with doxorubicin with or without mitomycin C</td>
<td>70.6%</td>
<td>25</td>
</tr>
<tr>
<td>Feldman et al, 2004</td>
<td>9</td>
<td>Primary HCC and intrahepatic cholangiocarcinoma</td>
<td>0%</td>
<td>Hyperthermic IHP (melphalan with or without TNF)</td>
<td>67%</td>
<td>16.3</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCC, hepatocellular carcinoma; OS, overall survival; PIHP, percutaneous isolated hepatic perfusion.


### Table 3
Selected studies of isolated hepatic perfusion in liver metastases of colorectal origin

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Study Details</th>
<th>IHP Agent</th>
<th>ORR</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinelli et al, 1996</td>
<td>9</td>
<td>Phase 1 trial</td>
<td>Mitomycin C</td>
<td>22%</td>
<td>17</td>
</tr>
<tr>
<td>Vahrmeijer et al, 2000</td>
<td>24</td>
<td>Phase 1 trial</td>
<td>Melphalan</td>
<td>29%</td>
<td>19</td>
</tr>
<tr>
<td>Alexander et al, 2002</td>
<td>7</td>
<td>Failed systemic and HAI therapy</td>
<td>Hyperthermia Melphalan/TNF/both</td>
<td>71%</td>
<td>19.7</td>
</tr>
<tr>
<td>Rothbarth et al, 2003</td>
<td>73</td>
<td>27% underwent adjuvant therapy after primary resection</td>
<td>High-dose melphalan</td>
<td>59%</td>
<td>28.8</td>
</tr>
<tr>
<td>Alexander et al, 2005</td>
<td>25</td>
<td>Failed first-line irinotecan therapy</td>
<td>Hyperthermia Melphalan</td>
<td>60%</td>
<td>12</td>
</tr>
<tr>
<td>van Iersel et al, 2007</td>
<td>30</td>
<td>53% received prior chemotherapy</td>
<td>Melphalan (IHP + HAI)</td>
<td>50%</td>
<td>27.8</td>
</tr>
<tr>
<td>van Iersel et al, 2008</td>
<td>105</td>
<td>48% patients had pre-IHP chemotherapy</td>
<td>Melphalan</td>
<td>50%</td>
<td>24.8</td>
</tr>
<tr>
<td>Zeh et al, 2009</td>
<td>13</td>
<td>Phase 1 trial for patients scheduled for HAI</td>
<td>Hyperthermia Oxaliplatin</td>
<td>66%</td>
<td>25</td>
</tr>
<tr>
<td>Alexander et al, 2009</td>
<td>120</td>
<td>80% received prior chemotherapy</td>
<td>Hyperthermia Melphalan/TNF/both</td>
<td>61%</td>
<td>17.4</td>
</tr>
<tr>
<td>Magge et al, 2013</td>
<td>12</td>
<td>Patients scheduled for HAI and with prior chemotherapy</td>
<td>Oxaliplatin + 5-FU</td>
<td>82%</td>
<td>Not reached*</td>
</tr>
</tbody>
</table>

**Abbreviation:** OS, overall survival.

*Median survival not reached at a median follow-up of 24 months.

*Data from* Refs. 27,33–41
SUMMARY

IHP relies on vascular isolation of the liver to deliver cytotoxic therapy with limited systemic leakage. Although promising results have been seen in the management of ocular melanoma and colorectal liver metastases, its morbidity and the need for specialized expertise have limited widespread use of the therapy. Advances in perfusion techniques including PHP (or chemosaturation) and prophylactic perfusion may provide exciting new avenues.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.suc.2015.12.005.

REFERENCES


