

Isolated Hypoxic Hepatic Perfusion with Retrograde Outflow in Patients with Irresectable Liver Metastases; A New Simplified Technique in Isolated Hepatic Perfusion

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Background: Isolated hepatic perfusion with high-dose chemotherapy is a treatment option for patients with irresectable metastases confined to the liver. Prolonged local control and impact on survival have been claimed. Major drawbacks are magnitude and costs of the procedure. We developed an isolated hypoxic hepatic perfusion (IHHP) with retrograde outflow without the need for a heart-lung machine.

Patients and Methods: Twenty-four consecutive patients with irresectable metastases of various origins were treated. IHHP inflow was via the hepatic artery, outflow via the portal vein with occlusion of the retrohepatic caval vein. Radiolabeled albumine was used for leakage monitoring. Melphalan was used at 1–2 mg/kg. A 25-minute perfusion period was followed by a complete washout. Local and systemic melphalan concentrations were determined.

Results: Compared with oxygenated classical IHP, the IHPP procedure reduced operation time from > 8 h to 4 hours, blood loss from > 4000 to 900 cc and saved material and personnel costs. Leakage was 0% with negligible systemic toxicity and 0% perioperative mortality. Tumor response: complete response (CR) in 4%, partial response (PR) in 58%, and stable disease (SD) in 13%. Median time to progression was 9 months (2–24 months); pharmacokinetics demonstrated intrahepatic melphalan concentrations more than 9 fold higher than postperfusion systemic concentrations.

Conclusions: IHPP is a relatively simple procedure with reduced costs, reduced blood loss, no mortality, limited toxicity, and response rates comparable to classic IHP. The median duration of 9 months of tumor control should be improved. Hereto, vasoactive drugs, will be explored in further studies.

Key Words: Isolated hepatic perfusion—Retrograde outflow—Hypoxic—Metastasis—Melphalan.

Approximately 50–60% of colorectal cancer patients will develop liver metastases during follow-up. In nearly a quarter of these patients the liver is the only

site of disease.¹ If hepatic metastases of colorectal cancer are resectable, 5-year survival rates are reported between 25% and 45% depending on several prognostic factors.² Patients with irresectable hepatic metastases have a 0–2% 5-year survival rate and a median survival of 10 months without treatment.³ Therefore, aggressive, selective treatment of the liver

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seems justified since control of hepatic metastases translates into improved overall survival. Despite the increasing response rates with systemic chemotherapeutic agents such as oxaliplatin and irinotecan in combination with 5-FU and the promising results with the addition of angiogenesis inhibitors,⁴ overall survival remains poor.^{5,6} In order to improve responses and survival, locoregional chemotherapeutic regimens have been developed. These therapies include hepatic arterial embolization, intratumoral injections of ethanol, acetic acid, biological agents, stereotactic or intra-arterial radiotherapy, intralesional laser therapy, cryotherapy, radiofrequency ablation, and regional infusion or perfusion of chemotherapeutic drugs. The best approach for regional infusion of chemotherapeutics in the liver is unknown. Hepatic artery infusion (HAI), hepatic artery ligation with hepatic artery and portal vein infusion, or portal vein infusion have all been attempted. Of these modalities, HAI is the most widely applied form. A number of studies have been conducted comparing systemic chemotherapy with HAI, and a modest but significant improvement of survival was demonstrated by HAI in a meta-analysis.⁷⁻⁹

In a leakage-free perfusion setting, isolated hepatic perfusion (IHP) shields the systemic compartment to drug exposure, and in combination with a washout procedure it protects against systemic toxicity. Clinical studies using melphalan with or without tumor necrosis factor alpha (TNF) have shown promising results.¹⁰⁻¹⁷ However, IHP is a major, complex, expensive, and time-consuming operation. These features in combination with hepatic and systemic toxicity are major drawbacks toward wide clinical application. Our aim was to develop an IHP that is easy to perform, with limited morbidity or mortality, not time consuming, and with minimal costs of the operation without affecting the antitumor efficacy. We started an isolated hypoxic hepatic perfusion (IHHP) technique with percutaneously placed balloon catheters and retrograde outflow without a heart-lung machine and extracorporeal venovenous bypass in pigs.¹⁸ In a recent study, we demonstrated the feasibility of this technique (retrograde outflow of the liver) in a clinical setting.¹⁷ A major drawback of the technique was 38% systemic leakage rate. On the basis of these results, we modified the technique by applying an "open" surgical procedure; balloon catheters are replaced by clamps and all tributaries to the vena cava such as the adrenal, lumbar, and diaphragmatic veins are dissected and ligated. Here we present the results of the first 24 patients with irresectable liver metastases who underwent an IHHP

with melphalan. The major difference between this new technique and the classic IHP is that there is no veno-veno bypass and heart-lung machine involved and the drainage of the liver is retrograde through the portal vein.

MATERIALS AND METHODS

Patient Selection Criteria

Inclusion criteria were as described previously.¹⁷ In all patients a radical resection of the primary tumor was performed prior to entering the study protocol except for one patient with hepatic metastasis of unknown primary. The liver metastases were considered irresectable, on the basis of multiple lesions in multiple segments of the liver and/or location near vascular structures. Tumor involvement had to be less than 50% of the total liver volume to prevent massive necrosis in case of a response. Absence of extra hepatic tumor growth was evaluated by computed tomography (CT) scan of thorax and abdomen. All patients had a Karnofsky performance score of at least 90, liver enzymes (ALAT, ASAT and AF) not higher than five times the normal values, and bilirubin not higher than two times the normal values. Exclusion criteria included: age younger than 18 or older than 70, portal hypertension, significant central nervous system disease, significant cardiovascular, pulmonary or renal disease, uncontrolled infections, presence of organ grafts, and chemotherapy or radiation therapy within 4 weeks prior to the IHHP. Routinely, an angiography was performed to exclude aberrant hepatic arteries or to visualize other anatomic anomalies. The study protocol was approved by the Medical Ethical Committee of the Erasmus University Medical Centre, and written informed consent was obtained from all patients.

Perfusion Circuit

Perfusion sets (PfM, GmbH, Cologne, Germany) consisted of a tubing set with a volume of 220 mL, containing a bubble trap. All IHHPs were performed with inflow via the hepatic artery and outflow via portal vein. In the perfusion circuit, flow was maintained by a roller pump and pressure was measured via a sideline.

Drugs

A dosage of 1 mg/kg melphalan (L-Pam, Alkeran, Wellcome Ltd. London, UK) was used in 20 of the 24

patients and infused through a sideline into the perfusion circuit. Two times 1.5 mg/kg melphalan and two times 2.0 mg/kg was used. In the first eight patients, a bolus infusion was used. In the last 16 patients, a 10-minute pump infusion was used. The total perfusion (10-minute infusion included) with melphalan was conducted for 20 to 30 minutes.

Surgical Procedure of the Retrograde Flow IHHP

A right subcostal incision was performed, and the liver was mobilized from its retroperitoneal and diaphragmatic attachments. A prophylactic cholecystectomy was not performed routinely. Tributaries to the vena cava such as the adrenal, lumbar, and diaphragmatic veins were dissected and ligated. The vena cava was isolated and clamped above and below the liver, respectively, to prevent venous leakage. The portal vein, proper hepatic artery, and gastroduodenal artery were dissected, and the hepatic artery cannulated via the gastroduodenal artery with an 8 F catheter for inflow of the perfusate. In two patients, an aberrant left hepatic artery, coming from the left gastric artery was cannulated together with the proper hepatic artery for inflow. The portal vein was cannulated with a 14 F catheter for outflow. Patients subsequently received 2 mg/kg heparin. The hepatic artery catheter and the portal vein catheter were connected to the perfusion circuit primed with 220 mL Haemaccel (Behring Pharma, Amsterdam, The Netherlands). After clamping of the caval vein superior and inferior of the liver, clamping of the aorta just beneath the diaphragm, clamping the portal vein just above the pancreas, clamping the proper hepatic artery just proximal of the gastroduodenal branch, and clamping of the common bile duct with its surrounding tissue, the retrograde isolated perfusion was performed. The retrograde perfusion setup is depicted in Fig. 1.

The perfusate was circulated by a constant flow. Stable perfusion was monitored by pressure measurement and the perfusate level in the bubble trap. Hereafter, melphalan was infused into the circuit and the perfusion was conducted for 20 to 30 minutes. Thereafter, a washout procedure was performed by 1 L of Haemaccel collecting the venous effluent. Total liver ischemia time never exceeded 60 minutes.

The isolation was terminated by relief of the clamps on the caval vein followed by the relief of the aortic clamp, controlling systemic blood pressure. The catheter in the hepatic artery could be removed and the gastroduodenal artery could be ligated followed by decanulation and closing the venotomy of

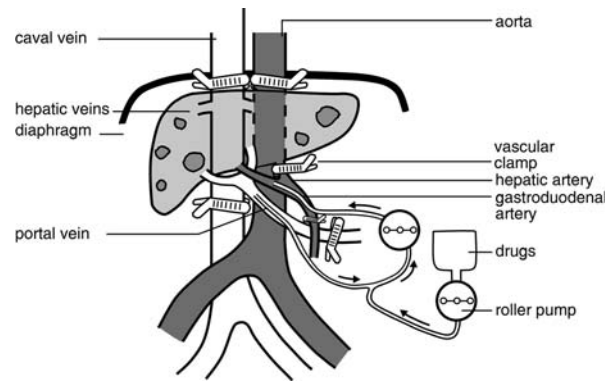


FIG. 1. The retrograde perfusion setup.

the portal vein. In case of an aberrant left hepatic artery, this artery was ligated after removal of the catheter.

Leakage Monitoring

During IHHP, potential leakage of drugs was monitored using a radioactive tracer. A small calibration dose of human serum albumin radiolabeled with ^{131}I was injected into the systemic circulation prior to the perfusion and 10-fold higher dose of the same isotope was injected into the isolated hepatic perfusion circuit. Continuous monitoring was performed with a precordial scintillation probe. Systemic leakage is expressed quantitatively as a percentage (100% leakage representing a homogeneous distribution of the isotope in the body).¹⁴

Blood Sampling

Before, during, and after the perfusion blood samples were taken and collected to study pharmacokinetics of melphalan and hematological, renal, hepatic, and gastrointestinal toxic side effects. Toxicity is graded according to the standardized WHO common toxicity criteria.¹⁹

Measurement of Melphalan Concentrations

Melphalan was measured in plasma by gas chromatography–mass spectrometry (GC-MS). P-[Bis(2-chloroethyl)amino]-phenylacetic acid methyl ester was used as an internal standard. Samples were extracted over trifunctional C18 silica columns. After elution with methanol and evaporation, the compounds were derivatized with trifluoroacetic anhydride and diazomethane in ether. The stable derivatives were separated on a methyl phenyl siloxane GC

TABLE 1. Characteristics of 24 patients with irresectable liver metastases treated by IHHP with retrograde outflow via portal vein with melphalan

PT	Tumor primary	Progressive on chemotherapy	Toxicity			Response after perfusion	Time to progr. (months)	Status	Months after perfusion
			Hepato	Blood	Renal				
1	CRC	No	1	0	0	CR	10	Alive	46
2	CRC	No	1	0	0	PR	24	Dead	38
3	CRC	Yes	1	4	0	SD	12	Dead	42
4	CRC	No	1	0	0	PR	6	Dead	29
5	CRC	No	1	3	0	PR	20	Dead	32
6	EM	No	1	0	0	PR	5	Dead	9
7	SARC	No	1	3	0	PR	13	Dead	17
8	CRC	No	2	0	0	PR	9	Dead	9
9	CRC	Yes	1	0	0	SD	12	Dead	37
10	CRC	Yes	1	0	0	PD	2	Dead	10
11	CRC	No	1	0	0	PR	9	Dead	29
12	CRC	No	1	0	0	PD	9	Dead	18
13	CRC	No	1	0	0	PD	2	Dead	8
14	CRC	Yes	1	0	0	PR	4	Dead	18
15	EM	No	1	0	0	PR	5	Dead	6
16	CRC	No	1	2	0	PR	9	Alive	29
17	UP	Yes	1	3	0	PD	2	Dead	5
18	EM	No	1	0	0	PR	9	Dead	20
19	CRC	No	2	2	0	PR	4	Dead	6
20	CRC	No	1	0	1	PR	5	Dead	5
21	EM	No	1	2	0	PR	13	Dead	15
22	CRC	Yes	1	0	0	PD	4	Dead	6
23	CRC	Yes	1	0	0	SD	5	Dead	6
24	CRC	Yes	1	0	0	PD	9	Alive	11

PT, patient number; CRC, colorectal cancer; CR, complete response; SARC, sarcoma; PR, partial response; EM, eye melanoma; SD, stable disease; UP, unknown primary; PD, progressive disease.

capillary column and measured selectively by single ion monitoring GC-MS in the positive EI mode described earlier by Tjaden et al.²⁰

Assessment of Tumor Response

This was done by comparing pre-perfusion CT and/or MRI scans of the liver with scans made at 8–10 weeks after IHHP. The tumor marker carcinoembryonic antigen (CEA) was monitored (when indicated) preoperatively and 8–10 weeks postperfusion, but was not used for response assessment. Clinical responses are assessed by standardized WHO criteria.¹⁹

RESULTS

Patient Characteristics (Table 1)

In a total of 24 consecutive patients, 13 males and 11 females with a median age of 57 years (range, 41–70) were included in the protocol. Eighteen patients had irresectable metastases of colorectal origin, four

ocular melanomas, one sarcomas, and one unknown primary hepatic metastases.

Operation Characteristics

Median operation time was 240 minutes (150–300 minutes), including perfusion time. Median blood and fluid loss was 900 mL (300–3200 mL). In the first eight patients, melphalan was administered as a bolus into the isolated liver circuit. The last 16 patients received a 10-minute pump infusion of melphalan. The perfusion (10-minute infusion included) with melphalan was conducted for 20 to 30 minutes. Perioperative mortality (<90 days) was 0%. Median hospital stay was 9 days (5–29 days).

Leakage Control

All IHHPs were leakage free during the perfusion except in one patient, where 2% systemic leakage was measured. When this perfusion was finished, it appeared that in this patient there was an insufficient clamping of the suprahepatic caval vein. After washout of the isolated circuit with Haemacell, a median of 7% (4–10%) leakage into the systemic

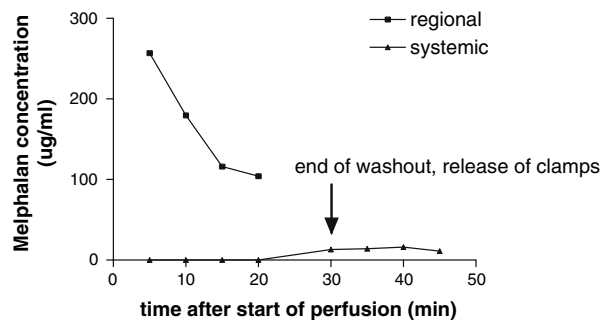


FIG. 2. Drug-concentration versus time curve.

circuit was demonstrated by continued monitoring until the end of the operation.

Toxicity Study (Table 1)

Hepatic toxicity consisted mainly of a transient rise of liver enzymes during the first week after IHHP. WHO grade I occurred in 92% of the patients (22 of 24) and WHO grade II in 8% of the patients (2 of 24). Three patients experienced bile duct necrosis (discussed in detail in the section “Complications”). No other hepatic toxicities occurred (no coagulopathy was observed). Systemic toxicity was mainly leucopenia, WHO grade I–III in 25% (6 of 24), and severe grade IV leucopenia in one patient (4%) after perfusion. Two of these patients received G-CSF (Neupogen, Amgen B.V., Breda, The Netherlands). One patient received prophylactic G-CSF. Eighteen patients (71%) did not develop leucopenia. No renal (except for one patient grade 1) or gastrointestinal toxicity was observed.

Melphalan Pharmacokinetics

Figure 2 shows a drug concentration vs time curve in the isolated circuit in a patient with a pump infusion. The area under the concentration versus time curve (AUC) calculation showed a regional concentration of 2382 ($\mu\text{g} \times \text{min}/\text{mL}$) versus undetectable systemic that makes the ratio AUC regional/systemic infinite (Fig. II). The median peak regional melphalan concentration was 68.04 $\mu\text{g}/\text{mL}$ (range, 42.3–256.99) and negligibly low to undetectable systemic concentrations. After washout and subsequent releasing of the clamps, median peak systemic 4.2 $\mu\text{g}/\text{mL}$ (range, 3.00–18.33) melphalan concentrations were observed. The AUC calculation showed a systemic concentration of 275 $\mu\text{g} \times \text{min}/\text{mL}$ after washout. Thus, intrahepatic melphalan concentra-

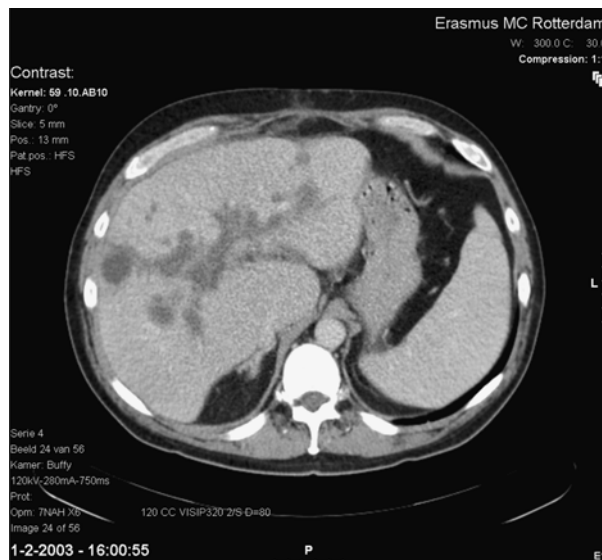


FIG. 3. Intra-hepatic bile duct necrosis after IHHP

tions during the IHHP are >9 fold higher than the post-IHHP systemic melphalan concentrations.

Complications

In three patients, bile duct necrosis occurred (Fig. 3). One of these patients was asymptomatic, and bile duct necrosis was found on routine CT scan during follow-up. Two of the patients with bile duct necrosis developed fever. No other explanation could be found for the fever, besides the intrahepatic “bilomas,” and therefore one patient was treated with percutaneous drainage and endoscopic stent placement in ductus choledochus. The other patient with fever received antibiotics. Both patients recovered, and slight elevations of bilirubin persisted, without complaints. In the first eight patients melphalan was administered as a bolus into the isolated liver circuit. After four patients melphalan dose was increased to 1.5 mg/kg in two patients and to 2 mg/kg melphalan in another two patients. Three of these patients (37.5%) developed bile duct necrosis, which is why the other 16 patients were treated with 1 mg/kg melphalan using a 10-minute pump infusion into the circuit. Bile duct necrosis did not occur in these patients. Postoperative chemical cholecystitis was not demonstrated.

Tumor Response and Patient Survival (Table 1)

In one patient a complete response was observed (4%). Partial response (PR) was seen in 14 patients

(58%), and stable disease (SD) was demonstrated in three patients (13%). Overall, a clinical response rate of 62% and a clinical benefit of nonprogression in 75% were observed. Six patients developed progressive disease (25%). Progressive disease occurred with median interval after IHHP of 9 months (range 2–24 months). Sixteen patients had progression of the liver tumors during follow-up. Fourteen patients developed extrahepatic disease during follow-up. To analyze the response rates and survival, it may be more opportune to include only the 18 patients with colorectal liver metastases. Median follow-up was 18 months. Median patient survival for patients with colorectal liver metastases ($n = 18$) was 18 months (range, 5–46 months). Median time to progression was 9 months (2–16 months). Seven of these 18 patients experienced failures of systemic chemotherapy. Two patients (PtNo 3 and 23) were progressive on the combination of 5-fluorouracil (5FU) and oxaliplatin (FOLFOX) (10 and 6 cycles, respectively), two patients (PtNo 9 and 10) were progressive on 5-FU and leucovorine (22 and 16 cycles, respectively), one patient (PtNo 14) was progressive after Xeloda (four cycles) and irinotecan (four cycles), one patient (PtNo 24) after six cycles of FOLFOX and four cycles of irinotecan, and one patient (PtNo 22) was progressive after Xeloda (six cycles), irinotecan (six cycles), and combination of Xeloda and oxaliplatin (XELOX) (eight cycles). Median survival for patients with colorectal liver metastases, not treated with chemotherapy before IHP ($n = 11$), was 29 months (range, 5–46 months).

DISCUSSION

Isolated liver perfusions are only performed by a few centers worldwide, demonstrating promising antitumor effects; however, the technique is a major, complex, expensive, and time-consuming operation. In the present study we describe an alternative technique using a retrograde hepatic flow in an isolated hypoxic hepatic perfusion (IHHP) system. The technique was performed in 24 patients and demonstrated to be safe, with minimal morbidity and no mortality. Overall response rate was 62% with no progression in 75%, and median time to progression of disease was 9 months.

The magnitude of the standard isolated liver perfusion technique is well demonstrated in two recently published series by the centers with the largest experience in IHP (NCI, Bethesda, MD, USA, and LUMC, Leiden, The Netherlands, respectively).^{11,15}

Median IHP operation time was reported to be more than 8 hours (range, 5.8–14.7 hours). In the study of Bartlett et al.¹¹ the estimated blood loss was 2.2 L (range, 0.8–4.5 L), and Rothbarth et al.¹⁵ reported a range of 0.9–10 L (median not given, older series mean of 4.4 L). Mortality (<30 days) occurred in both series with 5.6% in the Leiden series ($n = 71$) and 4% in the NCI series ($n = 124$). Classical IHP uses a venovenous bypass and a heart-lung machine, which is a time-consuming procedure necessitating a specialized perfusion team. In the present study a modification was developed, allowing a safe perfusion in a shorter operation time (median duration, 4 hour), with less blood loss (median, 900 cc), reducing morbidity and without mortality, without the need of a heart-lung machine or venovenous bypass.

The absence of mortality (<90 days) in the present study can be explained by the smaller number of patients and/or patient selection. However, it may well be related to the smaller magnitude of the operation and the corresponding decreased operation time and blood loss. Median hospital stay was 9 days (range, 5–29), which was also shorter than the 12 and 11 days in the aforementioned studies.^{11,15}

Hepatic toxicity is remarkably low in the present series except for three patients who developed bile duct necrosis (Table 1). High peak concentrations of melphalan in the isolated circuit might explain the bile duct necrosis that was observed in patients who were perfused with higher melphalan concentrations. In a preclinical study, the occurrence of severe cholangiofibrosis was strongly dependent on the melphalan concentration.²¹ The study also demonstrated that tumor response was not affected by melphalan peak concentration, but by the total dose of melphalan. Therefore, to prevent high peak concentrations keeping the same concentration of melphalan, bolus infusions were replaced by a 10-minute pump infusion. This resulted in the absence of bile duct necrosis in the last 16 perfused patients.

The maximum period of 60-minute hypoxia did not seem to result in extrahepatic and/or systemic toxicity. Moreover, clamping of the aorta just underneath the diaphragm for a maximum of 60 minutes did not lead to renal and/or gastrointestinal morbidity.

To overcome the use of a venovenous bypass and heart-lung machine, we performed a hypoxic perfusion. The use of hypoxia might also enhance the antitumor effect. Hypoxia renders tumor cells more sensitive to cytostatic agents in general and enhances the antitumor effects of drugs such as melphalan.^{22,23} Changing the perfusion direction may reduce liver toxicity, without affecting the antitumor efficacy as

described by Rothbarth et al.²⁴ An animal study demonstrated an unaffected tumor uptake and a reduced liver uptake by 80% in an IHP model with arterial inflow and retrograde portal outflow.²⁵ This may explain our remarkably low hepatic toxicity in the present series using retrograde outflow in a clinical setting.

In the large IHP series of patients with colorectal liver metastasis, response rates of 74% and 59%,^{11,15} respectively, are reported, which is in line with the response rate in the present study. The median time to progression in these IHP studies was 14.5 and 7.7 months, respectively. The time to tumor progression of 9 months after IHHP seems to be comparable to these numbers. Alexander et al. published their results in patients with progressive disease after irinotecan-based therapies, and still a response rate of 60% was obtained after IHP with melphalan.¹⁶ The 2-year survival was 28% with a 12-month median survival. Although interpretation and comparison of the results from these different studies are difficult, the results of the retrograde IHHP technique described here are similar. In the past 10 years, new anticancer agents (oxaliplatin and irinotecan) have increased the response and survival rates. The addition of targeted therapies (cetuximab and bevacuzimab) may increase the response rates more than 70%. Especially in this era of exciting developments, tailored treatment to increase individual survival rates while keeping the toxic effects to a minimum is challenging. The role of IHP in colorectal liver metastases has been discussed in recent reviews.^{24,26,27} The promising results of the IHP studies in the past years cannot be disregarded. It is conceivable to combine IHP with adjuvant treatment strategies to reduce the recurrence rate, which is the major determinant of the survival rate after IHP. Continuing locoregional treatment by HAI after an IHP procedure is technically feasible and appears to prolong the duration of the response and survival in patients with colorectal hepatic metastases.¹¹ Of the 18 patients with colorectal liver metastases in the present series, 10 developed extrahepatic disease, suggesting the need for additional systemic treatment. Duration of tumor control needs to be improved. To achieve this, the addition of vasoactive drugs, identified in our laboratory to have synergistic activity in combination with melphalan by significantly increasing drug uptake in the metastases, will be explored in further studies.^{28,29} At this time, IHHP should be reserved for those patients who are progressive on standard chemotherapy protocols. When responses in future trials are improved, this technique might be optional for patients who prefer a single procedure, which could potentially

lead to similar results as multiple courses of systemic or intra-arterial chemotherapy. Leaving behind at the end of the IHHP a port-a-cath system for subsequent HAI in case of (re)progression should also be considered as a strategy to further improve prolonged locoregional tumor control.

In ocular melanoma, the liver is the only organ site involved in 70–80% of patients and is usually responsible for death.^{30,31} The prognosis of a patient with hepatic metastases from uveal melanoma is extremely poor, with a median survival between 2 and 5 months.³² Partial liver resection is seldom possible. The therapeutic options are not very effective with systemic chemotherapy, providing 9% partial responses and no survival benefit.^{33,34} There is limited experience with IHP for hepatic metastases from uveal melanoma, but the response rates are promising.^{35–37} Despite the fact that the experience with hepatic metastases from uveal melanoma is small in the present study ($n = 4$), IHP seems to be an effective treatment. All four patients died because of progressive tumor growth and consequent liver failure after 6, 9, 15, and 20 months. Therefore, especially in this group of patients, local tumor control is likely to result in a survival benefit.

CONCLUSIONS

Isolated hypoxic hepatic perfusion with retrograde outflow via portal vein is a promising technique that is a relatively simple procedure with reduced blood loss, no mortality, very limited toxicity, and response rates comparable to classic, extensive IHP. The operation time is reduced to 4 hours, without the need of a heart-lung machine and perfusionists, which reduces the costs.

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