

# Isolated Hepatic Perfusion for the Treatment of Patients With Colorectal Cancer Liver Metastases After Irinotecan-Based Therapy

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**Background:** Irinotecan given with 5-fluorouracil and leucovorin is currently used as first-line therapy for patients with metastatic colorectal cancer (CRC). However, the response duration is <1 year, and second-line systemic chemotherapy has limited efficacy. We analyzed the efficacy of isolated hepatic perfusion (IHP) for patients with progressive CRC liver metastases after irinotecan.

**Methods:** Between March 1993 and February 2003, 124 patients with CRC liver metastases underwent IHP on institutional review board–approved protocols. The overall treatment mortality was 4% (5 of 124). Twenty-five patients (10 women and 15 men; mean age, 53 years) were identified who had progressive liver metastases by carcinoembryonic antigen, imaging studies, or both after irinotecan. A 1-hour hyperthermic IHP (mean hepatic temperature, 40.0°C) with melphalan 1.5 mg/kg (mean total dose, 100 mg) was administered via laparotomy. Perfusion with an oxygenated extracorporeal circuit was established with inflow via a cannula in the gastroduodenal artery and common hepatic artery inflow occlusion. Outflow was via a cannula in an isolated segment of the inferior vena cava. During IHP, portal and inferior vena caval flow were shunted to the axillary vein. Patients were assessed for radiographical response, recurrence pattern, and survival.

**Results:** The mean number of prior irinotecan cycles in 25 patients was 6 (range, 2–14), and it was given primarily as second-line therapy. The median number of liver metastases before IHP was 10 (range, 1–50), and the median percentage of hepatic replacement by tumor was 25%. The mean operative time was 9 hours (range, 6–12 hours), and the median hospital stay was 11 days (range, 8–76 days). There was 1 complete response and there were 14 partial responses in 25 patients (60%), with a median duration of 12 months (range, 5–35 months). Disease progressed systemically in 13 of 25 patients at a median of 5 months (range, 3–16 months). The median overall survival was 12 months (range, 1–47 months), and the 2-year survival was 28%.

**Conclusions:** For patients with progressive CRC liver metastases after irinotecan, IHP has good efficacy in terms of response rate and duration. Continued evaluation of IHP with melphalan as second-line therapy in this clinical setting is justified.

**Key Words:** Metastatic colorectal cancer—Isolated hepatic perfusion—Liver metastases—Melphalan—Hyperthermia

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There are 150,000 new cases of colorectal cancer (CRC) diagnosed annually in the United States.<sup>1</sup> It is estimated that 20% to 40% of patients diagnosed with CRC—30,000 to 45,000 individuals annually—will develop liver metastases. Most of these patients will

have disease that is not resectable and that is the sole or dominant site of disease progression.<sup>2</sup> Systemic combination chemotherapies and hepatic arterial infusion (HAI) therapies have been extensively evaluated in clinical trials for patients with unresectable hepatic CRC metastases. 5-Fluorouracil (5-FU), leucovorin, and oxaliplatin (a third-generation platinum analog) or irinotecan (a topoisomerase inhibitor) have been administered in large random-assignment trials comparing efficacy and survival against 5-FU and leucovorin as first-line therapy for patients with metastatic CRC.<sup>3-5</sup> The results of these trials have demonstrated overall radiographical response rates between 39% and 50%, with a median duration of response of approximately 9 months. Irinotecan, 5-FU, and leucovorin, given with bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, have been reported to have an overall response rate of 45% and a mean response duration of 10.4 months.<sup>6</sup> A recently reported random assignment trial comparing HAI with a fluorodeoxyuridine (FUDR)-based regimen versus intravenous 5-FU-based intravenous chemotherapy as first-line treatment for patients with unresectable colorectal liver metastases showed an overall radiographical response rate of 48% in the HAI therapy arm, with a mean duration of response of 9.8 months and a median overall survival of 22.7 months.<sup>7</sup> Taken together, these data suggest that newer systemic chemotherapy regimens seem to have an efficacy and duration of response on a par with contemporaneous results with FUDR-based HAI therapy; however, responses with both systemic and regional regimens are almost always partial and temporary.

For individuals who experience disease progression confined to the liver after treatment with a new systemic chemotherapy regimen, treatment with an alternate systemic regimen may not have reasonable efficacy, and the question of which second-line therapy is most appropriate has become increasingly important. For example, systemic treatment with oxaliplatin-based chemotherapy in patients who have had tumor progression on an irinotecan-based regimen has only a 9.9% response rate and a median duration of response of 4.6 months.<sup>8</sup> The role of FUDR HAI therapy as second-line treatment for patients with metastatic CRC liver metastases has not been conclusively established, because there are conflicting data in the literature. In one study that evaluated HAI FUDR as second-line therapy for patients with metastatic CRC confined to the liver, there was an overall response rate of 74%. However, in this

cohort, systemic infusional irinotecan therapy was given in conjunction with HAI, and the precise contribution of each component is not known.<sup>9</sup> In a second study of 35 patients given HAI FUDR as a sole second-line treatment modality, the overall response rate was only 14%, with a median duration of response of 7 months.<sup>10</sup> Taken together, these data suggest that effective treatment options are needed for second-line therapy.

We and others have been evaluating the use of isolated hepatic perfusion (IHP) as a regional treatment modality for patients with unresectable liver metastases of various histologies. Using melphalan with or without tumor necrosis factor, overall response rates between 60% and 75% have been reported in patients with different types of tumor histologies.<sup>11-14</sup> On the basis of these considerations, we reasoned that it may be suitable as a second-line therapy for patients with metastatic CRC metastases confined to the liver who have experienced treatment failure from first-line therapy with newly approved systemic combination chemotherapy regimens. This study was undertaken to evaluate the utility of IHP specifically as a second-line therapy in a patient population that experiences progressive CRC liver metastases after treatment failure with irinotecan.

## PATIENTS AND METHODS

### Patient Population

From 1993 to 2003, 124 patients with CRC underwent IHP on sequential but related phase I, II, or III protocols approved by the institutional review board of the National Cancer Institute evaluating different treatment IHP parameters, the results of which have been reported previously.<sup>11,12,15</sup> Five (4%) of these 124 patients experienced operative mortality. Of the entire cohort, 25 individuals were identified who received previous irinotecan-based therapy with therapeutic intent for established CRC liver metastases confined to the liver. Patients in this analysis underwent treatment on studies evaluating the efficacy of a 60-minute hyperthermic IHP with melphalan 1.5 mg/kg alone according to ideal body weight, with a minimum total dose of 90 mg and a maximum total dose of 120 mg.

Standard staging studies including a computed tomography (CT) scan of the chest, abdomen, and pelvis; magnetic resonance imaging (MRI) of the liver; and, as clinically indicated, brain imaging or

bone scan. Eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1, a serum bilirubin level  $< 2.0$  mg/dL, a platelet count  $\geq 150,000$ /mL, and a serum creatinine level  $\leq 1.5$  mg/dL.

### Toxicity and Response

All patients were evaluated 6 weeks after treatment and at 3- to 4-month intervals thereafter. Responses were scored by comparing gadolinium-enhanced T1- or T2-weighted images on MRI or contrast-enhanced CT scans during follow-up with pretreatment images. A complete response was defined as the disappearance of all radiographical evidence of disease on CT scan or MRI. A partial response was defined as a  $\geq 50\%$  decrease in the sum of the products of the perpendicular diameters of all measurable lesions for 1 month without progression ( $> 25\%$ ) of any site; a minor response was defined as a 25% to 49% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Any patient with less than a partial response or a response of  $< 4$  weeks' duration was considered a nonresponder. The appearance of new lesions or a  $> 25\%$  increase after a partial response or a complete response was scored as progressive disease. Because the therapy was limited to the liver because and the entry criteria limited treatment to patients with hepatic-only disease, responses were assessed only on the measurable hepatic lesions. New lesions occurring outside the liver were scored separately from new lesions occurring within the liver.

The National Cancer Institute common toxicity criteria (version 2.0) were used for toxicity and adverse event scoring. A copy of the common toxicity criteria (version 2.0) is available online (<http://ctep.info.nih.gov>). In general, grade 1 or 2 toxicities represent mild and self-limiting adverse events, grade 3 or 4 toxicities represent those that may be life-threatening or need intervention, and grade 5 represents treatment-related mortality. Any acute grade  $\leq 4$  systemic toxicity that was corrected within 24 hours of IHP or hepatic toxicity that was corrected within 7 days of IHP was not considered treatment related.

### Isolated Hepatic Perfusion

IHP was performed as described previously.<sup>15</sup> Briefly, via a laparotomy, the liver was extensively mobilized, the inferior vena cava was isolated, and the porta hepatis structures were completely dissected

and prepared for cannulation. After heparinization, cannulas were inserted into the saphenous, portal, and axillary veins for venovenous bypass, and the IHP circuit was connected to cannulas positioned in the gastroduodenal artery and an isolated segment of the retrohepatic inferior vena cava. Melphalan was obtained from Glaxo-Wellcome (Research Triangle Park, NC); 1.5 mg/kg was added over 3 to 5 minutes to the arterial inflow line of the perfusion circuit, and IHP was continued for 60 minutes. After IHP, the liver was flushed with crystalloid and colloid solution, and physiological blood flow was reestablished promptly to the liver.

A second cohort of patients also had a catheter placed into the gastroduodenal artery for intra-arterial therapy that was connected to a subcutaneous port for percutaneous access at the completion of the perfusion. Four to 6 weeks after the IHP, patients in the second cohort began infusional FUDR (.2 mg/kg/day) and leucovorin (15 mg/m<sup>2</sup>/day) given by continuous infusion via an external pump over 14 days monthly (2 weeks on therapy followed by 2 weeks off). Patients had their dose of FUDR reduced or held on the basis of toxicity from the prior dose. The monthly treatment continued for 12 months or until progression of disease, unacceptable toxicity, or technical problems.

### Statistical Analysis

All data are presented as mean and range unless otherwise specified. A comparison with a two-tailed  $P \leq .05$  was considered statistically significant.

## RESULTS

Demographics and tumor characteristics of the patient population are listed in Table 1. The median age of 53 years and the female/male distribution of 10:15, respectively, are consistent with this disease process. The mean number of cycles of irinotecan-based therapy given before referral was 6, and in most instances it was given as second-line therapy after prior treatment failure with 5-FU and leucovorin. Irinotecan was frequently given in combination with 5-FU and leucovorin in a treatment schedule as described by Saltz et al.<sup>16</sup> The cohort of patients treated with IHP as second-line therapy had a fairly advanced disease burden in the liver, as evidenced by a median number of metastases of 10 and a median percentage of hepatic replacement by tumor of 25%. Of note, the number of metastatic lesions in

**TABLE 1.** IHP for patients with colorectal liver metastases after irinotecan therapy

Variable	Data
CRC patients undergoing IHP from 1993 to 2003	124
Number of patients prescribed irinotecan	25
Age, y (range)	53 (32–72)
Female:male	10:15
Mean cycle no. for irinotecan (range)	6 (2–14)
First line	3
Second line	22
Medications before irinotecan	
FU/LV	20
FOLFOX	1
FUDR	1
No. metastatic lesions, median (range)	10 (1–50)
% Liver replaced by tumor, median (range)	25 (5–60)
< 25%	12
25%–30%	8
> 50%	5

CRC, colorectal cancer; IHP, isolated hepatic perfusion; FU, 5-fluorouracil; LV, leucovorin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FUDR, fluorodeoxyuridine.

the liver was assessed at laparotomy and in some circumstances was at variance with the number of lesions identified on preoperative imaging modalities. However, the percentage of hepatic replacement was assessed by using transaxial images of either T1-weighted gadolinium-enhanced MRI or contrast-enhanced CT, depending on which modality provided the most discrimination in determining the tumor margin from the unaffected hepatic parenchyma. The overall percentage of hepatic replacement was estimated by viewing sequential axial views of the imaging modalities.

The perfusion and operative data are listed in Table 2. The duration of the perfusion was 60 minutes, and the overall operative time reflects the significant amount of dissection necessary to ligate all sources of potential perfusate leak during treatment and prepare the vascular structures for cannulation. The cannulation time was typically quite short. The mean total melphalan dose was based on a formula of 1.5 mg/kg of ideal body weight, with a minimum and maximum amount of melphalan of 90 and 120 mg, respectively. Treatment was administered under hyperthermic conditions; target tissue temperatures were 39.5°C to 40.5°C. Central left and right hepatic temperatures were measured during perfusion. Heating was typically prompt, and temperatures were comparable, thus indicating uniform distribution of perfusate throughout the entire hepatic parenchyma. Flow rates were increased until perfusion pressures through the circuit were equal to or greater than the mean systemic arterial blood pressure and were usu-

**TABLE 2.** Perfusion and operative data

Variable	Data
Duration (min)	60
Melphalan dose (1.5 mg/kg) (mg)	100 (80–136)
Central liver temperature (°C)	40 (39–40.8)
Perfusion flow rate (mL/min)	773 (550–1100)
Perfusion pressure (mmHg)	141 (86–197)
Bypass flow rate (mL/min)	1888 (1300–2520)
Estimated blood loss (L)	2.2 (.8–4.5)
Operative time (h)	9 (6–12)
Median hospital stay, d (range)	11 (8–76)

ally considered to be physiologic or greater. During IHP, palpation of the hepatic artery proper was undertaken, and pressure within the vessel was estimated to typically be 10 to 20 mmHg or lower than that reflected in the perfusion circuit. This likely represents pressure artifact generated by flow of the perfusate through the 3-mm arterial inflow cannula. The venovenous bypass flow rates that shunted portal venous flow and infrahepatic inferior vena caval blood flow to the systemic circulation were almost 2 L/min and are thought to contribute to the hemodynamic stability that was observed during treatment. The estimated blood loss, operative time, and median hospital stay reflect the major nature of the operation.

Five mortalities (4%) have been associated with IHP in the entire cohort of colorectal patients (n = 124) treated over the past 10 years. Of those five, two occurred in patients who had been previously treated with irinotecan. However, on the basis of our experience, it does not seem that irinotecan treatment per se increases treatment risk with IHP.<sup>12,17</sup> Other reversible operative and treatment-related mortalities are listed in Table 3. There was one episode of self-limiting postoperative hemorrhage that required transfusion but immediately stabilized on correction of coagulopathy; three patients had pleural effusion; and one each experienced atrial fibrillation and transient abdominal ascites. Because high-dose melphalan is administered to the entire hepatic parenchyma, it is understandable that the vast majority of patients experience transient grade 3 or 4 hepatic-related toxicity. Other tumor-related toxicities were infrequent and included an increase in serum creatinine and thrombocytopenia each in two patients.

All responses were assessed with standard radiographical criteria, and although only 23 patients were assessable for response, overall response rates based on all 25 patients who underwent treatment were calculated (Table 4). There was one radiographical

**TABLE 3.** Postoperative and treatment-related morbidity

Variable	Data
Postoperative morbidity	
Bleeding	1 (4%)
Pleural effusion	3 (12%)
Atrial fibrillation	1 (4%)
Ascites	1 (4%)
Grade 3/4 treatment-related toxicity	
Bilirubin	9 (36%)
Transaminases	14 (56%)
Creatinine	2 (8%)
Platelets	2 (8%)

**TABLE 4.** Results of IHP in 25 colorectal cancer patients with isolated liver metastases after tumor progression on irinotecan

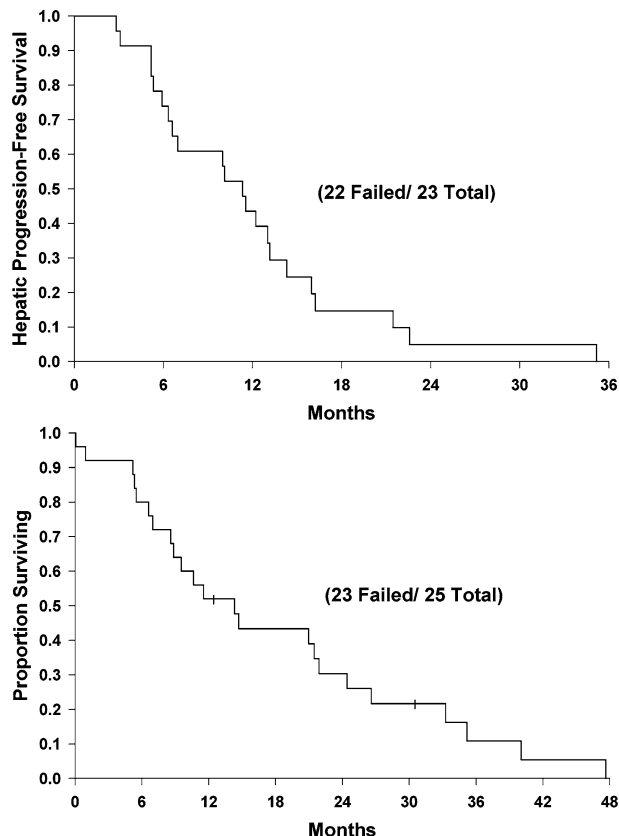
Group	n	Response <sup>a</sup>	Mean duration (mo)
Overall	25	15 (60%)	13.2 (5–35)
IHP alone	13	7 (54%)	8.6 (5–13)
IHP + HAI	12	8 (67%)	17.3 (11–35)

IHP, isolated hepatic perfusion; HAI, hepatic arterial infusion.

<sup>a</sup>All radiographical responses.

complete response, and there were 14 partial responses, for an overall response rate of 60% and a mean duration of response of 13.2 months. Because these individuals were treated on sequential but related IHP protocols, there was a cohort that received additional post-IHP therapy via HAI infusion of floxuridine (n = 12). Of these 12, 5 also received 3 cycles of 5-FU, leucovorin, and oxaliplatin as described by de Gramont et al.<sup>5</sup> In the 13 patients who underwent IHP alone, there were 7 partial responses, and in the group undergoing IHP with postoperative therapy, there were 8 responses. Although the overall response rates were not clearly different, the mean duration of response was substantially longer in individuals who received post-IHP therapy (Table 4).

The Kaplan-Meier actuarial hepatic progression-free survival in 23 patients assessable for response and the overall survival in the 25 patients who underwent treatment are shown in Fig. 1. The median hepatic progression-free and overall survivals were 12 months, and there was a 28% 2-year survival. Figure 2 shows a representative result in an individual undergoing IHP with multiple large hepatic metastases that progressed after irinotecan therapy. The top three panels show a pretreatment T1-weighted gadolinium-enhanced MRI scan demonstrating a large central lesion and a second large lesion in the inferior aspect of the right lobe. Twelve months after therapy, all lesions decreased significantly in size, and there was a central lucency in the

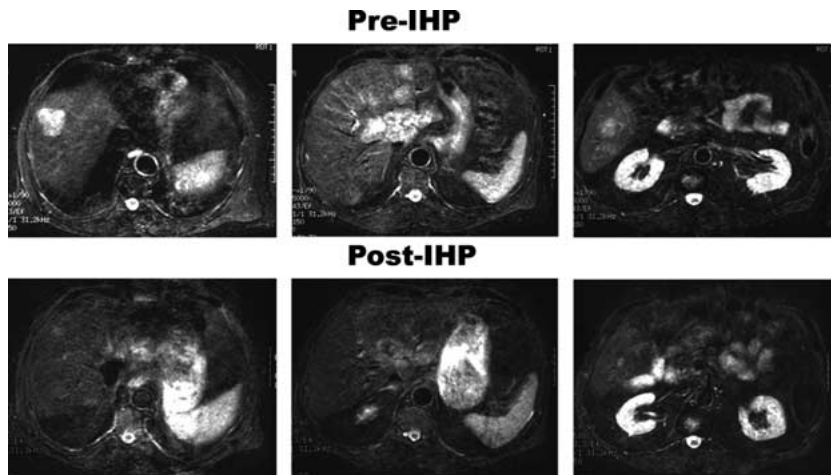


**FIG. 1.** Kaplan-Meier actuarial hepatic progression-free (top) and overall (bottom) survival in patients undergoing IHP for colorectal liver metastases after irinotecan-based therapy. The actuarial median survival for each was 12 months, and there was a 28% overall 2-year survival.

residual tumor bed—a characteristic finding in large lesions after this type of therapy.

## DISCUSSION

These data indicate that IHP with melphalan deserves continued clinical evaluation as second-line therapy for patients with metastatic CRC confined to the liver who experience progressive disease after treatment with irinotecan-based or other systemic chemotherapy regimens. Although this has not been evaluated in a systemic fashion, it seems that the addition of HAI to FUDR may prolong the duration of response. Despite previous treatment with high-dose combination chemotherapy, the incidence and severity of toxicities associated with the procedure do not seem to be different from previous experiences in patients who have undergone limited or no prior therapy. Almost all patients experience transient he-



**FIG. 2.** T1-weighted gadolinium-enhanced magnetic resonance imaging scan showing representative hepatic metastases in a patient who experienced tumor progression after 5-fluorouracil, leucovorin, and irinotecan (**top panels**) and comparable images obtained 1 year after isolated hepatic perfusion (IHP) with melphalan and 3 cycles of hepatic arterial infusion therapy with fluorodeoxyuridine showing a partial response (**bottom panels**) that was stable for 16 months.

hepatic toxicity manifested by significant but reversible increases in hepatic transaminases. This most likely represents a chemical hepatitis secondary to melphalan on the normal hepatic parenchyma. On the basis of the original large number and size of liver metastases that are present in patients referred for IHP, we have not frequently encountered an indication to resect residual hepatic disease even after the best response in the liver to IHP. In addition, there is considerable capsular fibrosis around the liver and porta hepatis after treatment that would make a segmental or lobar resection potentially dangerous. We have performed either a limited wedge excision or local ablation for solitary or limited residual masses in the liver in selected circumstances.

Because of the availability of multiple new agents for patients with metastatic CRC, first-line treatment with these agents has become more common. However, responses to newer combination systemic therapies are almost always partial and transient, and second-line therapies are emerging as a significant consideration. Oxaliplatin-based systemic chemotherapy in patients who have previously progressed through irinotecan-based chemotherapy is associated with a partial response rate of <10% and a median duration of response of <5 months.<sup>8</sup> These data suggest that the development of novel second-line treatment options remains important. For those whose disease progresses exclusively in liver, regional therapy options may be appropriate if sufficient efficacy can be demonstrated. We have previously shown that by using a standardized operative procedure, complete vascular isolation of the liver can be routinely achieved during IHP and, therefore, can serve as a regional delivery platform for novel therapeutics or biological agents that cannot be tolerated sys-

temically.<sup>15</sup> Certainly, as systemic therapy becomes increasingly effective, similar improvements in the efficacy of regional therapies must occur to justify their application in patients with isolated liver metastases. Recently, investigators have reported encouraging results with oxaliplatin administered via HAI for patients with colorectal liver metastases.<sup>18</sup> Whether this agent or other agents have utility in IHP is not known. Moreover, the selection of patients for regional therapy to the liver as second-line treatment is being performed in the context of a favorable selection bias for those who have not developed imageable extrahepatic metastatic disease. In that subset, effective hepatic regional therapy may translate into a meaningful improvement in survival.

IHP has not been directly compared with HAI floxuridine-based therapy for patients with metastatic CRC confined to the liver. Although both forms of therapy typically require laparotomy for treatment delivery or pump placement, morbidity associated with the latter procedure is less compared with IHP.<sup>19,20</sup> However, treatment is protracted over many months, and biliary toxicity, when it occurs, may not be reversible. The efficacy of HAI FUDR therapy as second-line treatment for patients with colorectal liver metastases has not been conclusively established. One study showed a response rate of 75% by using a combination of HAI FUDR and infusional systemic irinotecan, whereas another trial showed only a 14% response rate when HAI with floxuridine was used as a sole second-line treatment modality.<sup>9,10</sup> It is noteworthy that in this study, a combination of IHP and HAI resulted in a response duration of 17 months.

The major limitations to IHP are the complexity and expense associated with treatment, as well as the

fact that the current technique can be performed only one time. Percutaneous hepatic perfusion is a strategy to deliver regional therapy to the liver and hemofiltrate the hepatic venous effluent to remove the therapeutic agent by using percutaneously placed catheters in the hepatic artery and retrohepatic vena cava. Therapy can be administered for as many as eight cycles, and we have recently reported preliminary results with melphalan administered via this technique in patients with unresectable liver metastases.<sup>21</sup> As refinements in the technique of IHP address its current limitations, it may become a more routinely and widely accepted treatment option for patients with metastatic cancers confined to the liver.

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