Pharmacologic and clinical aspects of isolated hepatic perfusion (IHP) of liver metastases of solid tumours

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CHAPTER 4

Isolated hepatic melphalan perfusion of colorectal liver metastases: outcome and prognostic factors in 154 patients

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Abstract

The aim of this study was to identify prognostic factors for local and systemic failure after isolated hepatic perfusion (IHP) with 200 mg melphalan in patients with colorectal liver metastases.

Hundredandfifty-four patients were selected for IHP and underwent laparotomy. Patients were monitored for response, toxicity and survival. Univariate and multivariate analyses were performed to identify prognostic factors for hepatic response, progression-free and overall survival.

Hepatic response rate was 50% with a median progression free and overall survival of respectively 7.4 months and 24.8 months. In multivariate analyses, absence of ability to perfuse through the hepatic artery (P=.003), severe postoperative complications (P=.048) and more than 10 liver metastases (P=.006) adversely influenced overall survival and no adjuvant chemotherapy adversely influenced progression-free survival.

This is the first study to report prognostic factors for survival after IHP. Possibly, overall and disease-free survival can increase if preoperative screening is improved. In future studies on IHP, adjuvant chemotherapy should be considered.

Introduction

In approximately 30% of colorectal cancer patients the liver is the only site of metastatic disease [1, 2]. Complete surgical resection is considered the treatment of choice with 5-year survival rates ranging from 25-51%. However metastasectomy is only possible in less than 10 percent of patients due to the number, location or size of the metastases [3-5]. The management of irresectable colorectal liver metastases remains a challenge for both medical oncologists and surgeons. Recent studies have shown improved survival with the introduction of oxaliplatin, irinotecan, bevacizumab and cetuximab in the systemic treatment of colorectal metastases [6-11]. Regional treatment options however, can offer the potential benefit of both aggressive local treatment and limited systemic toxicity. Several regional therapies have been developed including radiofrequency ablation (RFA) and isolated hepatic perfusion (IHP). Phase II studies involving IHP in colorectal cancer patients have shown hepatic response rates up to 74% with a median time to hepatic progression up to 14.5 months, a median overall survival of 27 months and 5 year survival of 9%, establishing its value in the treatment of colorectal liver metastases[12-15]. While several studies have been published on prognostic factors in RFA, little is known about prognostic factors in IHP[16, 17]. Most IHP studies focus on local response rate and recurrence, but the at least equally important systemic (i.e. extrahepatic) failure is scarcely reported. The aim of this study was to evaluate both local and systemic failure after IHP with 200mg melphalan and identify possible prognostic factors in colorectal cancer patients.

Patients and methods

Patient Eligibility

In the 10-year period from August 1994 and December 2004, 179 patients with liver metastases were considered for treatment with 200mg melphalan, according to a study protocol approved by the medical ethical committee of the Leiden University Medical Center, as previously published [12, 18]. The data were obtained from a prospectively collected database and analyzed retrospectively. In 25 patients the primary tumor was of non-colorectal origin and these patients were excluded, leaving 154 patients for further analysis. Informed consent was obtained from all patients. All patients had measurable, irresectable colorectal metastases confined to the liver. Standard staging studies were performed including CT scan of the chest and abdomen. Additional MRI or PET scans were performed if clinically indicated. Eligibility criteria included a WHO performance status of 0 or 1, leukocyte count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, maximum

serum creatinine level 135 µmol/L, maximum bilirubin level 17 µmol/L and minimum albumin level 40 g/L. Exclusion criteria were age over 70 years, life expectancy of less than 4 months, more than 60 percent hepatic involvement of tumour tissue as estimated from the preoperative abdominal CT scan, coagulation disorders and evidence of extrahepatic metastatic disease. The interval between resection of the primary colorectal tumour and perfusion had to be at least 6 weeks.

IHP technique

Briefly, the liver was mobilized from the diaphragm through a transverse abdominal incision. The common hepatic artery (8-Fr 77008 one-piece pediatric arterial cannula; Medtronic, Minneapolis, Minnesota, USA) and the portal vein (12-Fr perfex perfusion catheter CH12; B. Braun Medical, Oss, The Netherlands) were cannulated and connected to a heart-lung machine which consisted of two independent roller pumps (model 10-30-00; Cobe/Stöckert, Munich, Germany). The inferior vena cava (IVC) was cross-clamped above the hepatic veins and cannulated proximal of the renal veins (Polystan 36 Fr, straight, A/S, Värlöse, Denmark) to allow undisturbed blood flow from the hepatic veins through the IVC towards the heart-lung machine. To isolate the hepatic circuit, tourniquets were secured around the hepatic artery, portal vein and IVC.

For the extracorporeal venovenous bypass, the right femoral vein (22-Fr cannula DI-ITF022L; Edwards Lifesciences, Irvine, California, USA) and the portal vein (17-Fr perfex perfusion catheter CH17; B. Braun) (proximal to the tourniquet) were cannulated and connected to the right axillary vein (18-Fr 7326 perfusion cannula; Lifestream International, The Woodlands, Texas, USA). The venovenous bypass was supported by a centrifugal pump (Medtronic BIO-Medicus, Eden Prairie, Minnesota, USA) and primed with 700 mL 0.9 % saline. The perfusion medium consisted of intrahepatically trapped blood and 1250 mL Gelofusine® (Vifor Medical, Sempach, Switzerland) plus 2500 units heparin (Leo Pharma, Breda, The Netherlands) to yield a final volume of approximately 2 liters. Throughout the 1-h perfusion interval, the perfusate was kept at a temperature of 39·5 °C by a heat exchanger and oxygenated using an oxygenator (Cobe VPCML; Cobe Cardiovascular, Arvada, Colorado, USA) except for the last patient who was oxygenated using a different oxygenator (Dideco D901, SORIN group Italia, Mirandola, Italy). After perfusion, the liver was flushed for approximately 10 minutes with 3 liters Gelofusine®. All cannulas and clamps were removed, and the incisions were closed. To prevent possible postoperative cholecystitis, cholecystectomy was performed.

Melphalan

Melphalan 200mg (Alkeran®, GlaxoSmithKline, Zeist, The Netherlands) was first dissolved in 40 mL Wellcome Diluent (a 60/40 (v/v) mixture of proylene glycol containing 5.2% (v/v) ethanol and 0·068 mol/l sodium citrate), which was subsequently diluted with 60 mL sterile saline. Melphalan was administered as a bolus in the isolated hepatic circuit and in the last 30 patients through 20 minute infusion using an infusionpump (Pilote Anesthesie; Fresenius, Brezins, France) connected to the hepatic artery line of the isolated hepatic circuit.

Leakage Detection

Leakage of perfusate into the systemic circuit was monitored by adding 10 MBq ^{99m}Tc-pertechnetate to the isolated circuit with subsequent measurement of the level of radioactivity in both the systemic and isolated circuit, as described previously [19, 20]. If no leakage was detected, melphalan was administered; if leakage was calculated to exceed 10% during the perfusion period, the procedure was stopped and the liver was flushed just before this level was reached.

Postoperative Care

All patients received a daily subcutaneous dose of 480 µg granulocyte colony-stimulating factor (G-CSF) (Filgrastim/Neupogen®; Amgen, Breda, The Netherlands) starting the day after the operation until the nadir in leukocyte count was reached and the count had risen to more than 1.0×10^9/L. Patients were monitored in the intensive care unit for at least 1 day after IHP. Liver and renal function tests and full blood counts were carried out daily in the first week and henceforth as indicated by their respective levels. Antibiotics in a combination of cefuroxim and metronidazol were given to all patients for 5 days after IHP.

Toxicity

Systemic and regional toxicity were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Hepatic toxicities were considered melphalan related, if elevations in liver function persisted beyond 7 days after perfusion, as previously suggested [13].

Response evaluation

Objective tumour response measurements were obtained by follow up CT scans of the liver and remaining abdomen at 3-month intervals after treatment and at 6-month intervals after 1 year. Additional imaging was performed if clinically indicated. All CT scans were reviewed using RECIST criteria to determine response rates. According to RECIST criteria lesions were only considered measurable if ≥10mm, complete response was defined as disappearance of all known disease, partial response as a reduction in the sum of maximal diameters of measurable lesions of ≥30%, stable disease as a reduction of <30% or an increase of <20% and progressive disease as an increase of ≥20% or the appearance of new intra- or extrahepatic lesions [21]. Disease-free survival was calculated from the date of IHP until the date of local and/or systemic recurrence or death from any cause.

Serum carcinoembryonic antigen (CEA) levels were determined prior to treatment and at all follow-up visits.

Statistics

All data were analyzed using SPSS (version 14.0) software and presented as mean +/- SD or median followed by the range. Survival was measured from the day of surgery until death or until the last day of follow up. Postoperative mortality was included in the response and survival analysis. For discrete variables univariate analysis was performed with the χ^2 test. Factors with $P < 0.10$ in univariate analysis were entered in the multivariate analysis using logistic regression. Odds ratios are reported with 95 percent confidence intervals. Overall survival and disease progression analysis was analyzed using Kaplan-Meier curves, the log-rank test was used to identify differences in survival between groups. Factors with $P < 0.10$ in univariate analysis were entered in the multivariate analysis using Cox's proportional hazards model. Hazard ratios are shown with 95 percent confidence intervals. All reported P values are two sided.

Results

Patient and treatment characteristics

Of the total of 154 colorectal cancer patients with unresectable liver metastases considered suitable for IHP, 105 (68%) were actually treated with IHP. At surgery 34 patients showed signs of extrahepatic disease not detected previously on imaging, 8 patients

showed more than 60 percent hepatic involvement of tumour tissue, 2 patients could not be treated due to a vascular anomaly and in 5 patients an isolated circuit could not be achieved due to excessive hemorrhage. After a median follow up of 85.4 months this group non-IHP patients showed a median overall survival of 10.1 months (range 1.6 – 66.2 months). They were excluded from further analysis. Demographics and tumour characteristics of the patients treated with IHP are listed in Table 1. Treatment parameters are

Table 1 Patient and tumour characteristics

Characteristic	n (%)
No. of patients	105
Sex	
Male	78 (74)
Female	27 (26)
Age	
<60 years	70 (67)
≥60 years	35 (33)
Liver metastases	
Synchronous	67 (64)
Metachronous	38 (36)
No. of metastases	
<10	71 (68)
≥10	34 (32)
Estimated % of viable liver tissue	
≥90%	56 (53)
<90% and >60%	34 (33)
≤60%	15 (14)
Localization of primary tumour	
Right sided colon	13 (12)
Left sided colon and rectum	92 (88)
Pretreatment CEA level	
Normal (≤3.0 µg/mL)	15 (14)
Raised (>3.0 µg/mL)	89 (85)
Unknown	1 (1)
Median duration from diagnosis of liver metastases to IHP (months), [range]	4.8 [0.9-34.4]
Prior treatment directed at liver metastases	51 (48.6)
Chemotherapy [a]	
– Single agent 5FU based regimens	44 (78.6)
– Oxaliplatin based regiments	
– Irinotecan based regiments	9 (16.1)
	3 (5.9)
Hepatic Surgery	
	4 (3.8)

[a] In total 56 lines of chemotherapy were given to a total of 51 patients.

shown in Table 2. In 10 patients the perfusion did not take place for the full 60 minutes due to leakage. Two patients were perfused for 50 minutes, 1 for 45 minutes, 4 for 30 minutes, 1 for 25 minutes and two for 10 minutes. Between August 1997 and December 2000 patients received standard advice to undergo adjuvant systemic treatment, which at that time was standard protocol for all local treatments of liver metastases at our center. Whether patients did actually undergo adjuvant systemic treatment depended upon patient wishes and if referred to other centers, local policy. Seventeen (16%) patients received adjuvant chemotherapy after IHP. Fourteen patients received 5-FU/ leucovorin based schedules, 2 patients received raltitrexed, while 1 patient was treated with irinotecan. Median follow up was 85.4 months (range 21.9 to 147.7 months).

Toxicity and complications

Six patients died within 30 days after IHP because of progressive liver failure and multi-organ failure and 1 more patient died 3 months after IHP due to a liver abscess, resulting in an operative mortality of 7%. Major complications are listed in Table 2. Systemic toxicities are listed in Table 3. Grade 3 or 4 hepatotoxicity was present in 41 (39%) patients.

Table 2 Treatment parameters

Parameter	Mean ± SD	n (%)
Perfusion		105
Hepatic artery and portal vein		99 (94)
Portal vein		6 (6)
Flow rate hepatic artery (mL/min)	337 ± 103	
Flow rate portal vein (mL/min)	294 ± 92	
pressure hepatic artery (mm/Hg)	105 ± 31	
pressure portal vein(mm/Hg)	33 ± 9	
Percentage leakage during perfusion	1.6 ± 2.3	
Blood loss (L)	5.7 ± 4.2	
Operative time (hr)	9.5 ± 1.5	
Hospital stay (days)	13 ± 7	
Perioperative mortality		7 (7)
Major complications		39 (37)
Veno-occlusive disease		9
Hepatic artery obstruction		2
Spleen rupture		3
Sepsis		2
Portal hypertension		2
Re-operation		11
Bleeding		9
Abscess		1
Ileus		1

Table 3 Toxicity according to National Cancer Institute Common Toxicity Criteria version 2.0 (n=105)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte nadir	71.4% (75)	8.6% (9)	8.6% (9)	3.3% (1)	6.7% (2)
Bilirubin	39% (41)	32.4% (34)	10.5% (11)	11.4% (12)	6.7% (7)
Alkaline phosphatase	1.9% (2)	36.2% (38)	46.7% (49)	15.2% (16)	0% (0)
Alanine aminotransferase (ALAT)	13.3% (14)	38.1% (40)	28.6% (30)	18.1% (19)	1.9% (2)
Asparate aminotransferase (ASAT)	14.3% (15)	59% (62)	17.1% (18)	7.6% (8)	1.9% (2)

Sixteen (15%) patients experienced more than one grade 3 or 4 hepatotoxicity. Although some elevation persisted in the patients with either VOD or portal hypertension, the hepatotoxicity was transient in most patients. There was no significant difference in grade 3 or 4 hepatotoxicity between patients with or without chemotherapeutic prior to IHP (449% v 56%; P=0.44).

Tumour response

Seventy-two (81%) of the 89 patients with previously elevated CEA levels experienced a normalization or reduction of 50% or more 1 to 3 months after perfusion with a median duration of response of 6.3 months (range 1.6 to 107.8 months).

Hepatic and overall treatment responses were measured by comparing follow-up CT scans to the pretreatment scan, according to RECIST criteria. As 7 patients died postoperatively and 1 patient died within 3 months of progressive bone metastases, 97 patients were eligible for measurement of tumour response. Hepatic response rate (complete and partial remission) was 50% (N=52/105) including 3 complete responses. Twenty-three patients (22%) had stable disease, whereas 22 patients (21%) immediately showed progressive disease. The median duration of hepatic response (complete and partial remission) was 11.4 months (range 5.2 to 108 months). Table 4 shows the results of univariate analysis for prognostic factors of hepatic response (complete or partial remission). Univariate analysis revealed that positive prognostic factors for hepatic response to IHP were female sex and adjuvant chemotherapy. Multivariate analysis confirmed the positive effect of adjuvant chemotherapy (odds ratio for complete or partial remission, 5.91; 95% CI, 1.54 to 22.6; P=.009), the effect of female sex was borderline significant (odds ratio for complete or partial remission, 2.65; 95% CI, 0.98 to 7.15; P=.05).

Table 4 Prognostic factors evaluated in univariate analysis in this study

	Hepatic Response		Progression-free survival (months)		Overall survival (months)	
Parameter	%	P	Median	P	median	P
Sex		.09		.86		.62
Male	49		7.3		24.8	
Female	68		7.7		21.3	
Age		.55		.10		.06
<60 years	52		7.6		26	
≥60 years	58		7.1		17.8	
Localization primary tumour		.11		.50		.17
Right sided	30		5		13.9	
Left sided	56		7.5		26	
No. of metastases		.35		.15		.01
<10	57		7.5		26.6	
≥10	47		6.9		17.2	
Estimated % of viable liver tissue ≥90%		.38		.55		.08
<90% and >60%	58		7.3		30.3	
≤60%	44		5.7		19	
	62		7.8		20.6	
Chemotherapy directed at liver metastases prior to IHP		.63		.09		.44
Yes	56		6.9		22.7	
No	51		7.7		28.1	
Perfusion technique		.88		.61		.002
Hepatic artery and portal vein perfusion	54		7.4		25	
No hepatic artery perfusion	50		3.3		5.9	
Postoperative complications		.86		.42		.03
Yes	53		6.9		16.9	
No	54		7.7		27.4	
Adjuvant chemotherapy		.01		.01		.23
Yes	82		13.6		33	
No	48		6.8		24.5	
Extrahepatic metastases prior to IHP		.30		-		.008
Yes						
No	33		-		13.2	
	55		-		25	

Factors with $P < 0.10$ in univariate analysis were entered in the multivariate analysis using logistic regression.

Local and systemic failure

One patient died 8 months after IHP of progressive cholestatis before progression occurred. As seven patients died postoperatively, 97 patients were available for response evaluation. All patients, except 4, showed progressive disease during follow up. The

median progression-free survival was 7.4 months (range 1.4 to 107.8 months). Of the progressive patients, 63 (68%) showed hepatic progression, 13 (14%) extrahepatic progression and 17 (18%) a combination of both hepatic and extrahepatic progression. Of the hepatic progressive patients, 14 (17%) showed new hepatic lesions, 27 (34%) showed an increase of preexistent hepatic lesions and 39 (49%) showed a combination of both. Extrahepatic progression occurred mainly in the lungs (43%), intra-abdominal lymph nodes (27%) and cerebrum (10%). Other locations included bones, mediastinal lymph nodes and abdominal wall. In retrospect 7 (7%) patients showed extrahepatic disease prior to IHP. Univariate analysis revealed that positive prognostic factors for progression-free survival were: no chemotherapy prior to IHP and adjuvant chemotherapy following IHP (P=.09 and P=.01, respectively; Table 4). Median progression-free survival was 13.6 months in the patients who received adjuvant chemotherapy, as compared to 6.8 months in the patients who were not treated with adjuvant chemotherapy (Figure 1). Cox multivariate analysis confirmed a statistically significant positive effect of adjuvant chemotherapy on progression-free survival (P=.039; Table 5)

Overall survival

Ten patients were still alive at the end of follow up. Seventy-nine (75%) patients received treatment directed at their metastases after progression following IHP. In total 73 (70%)

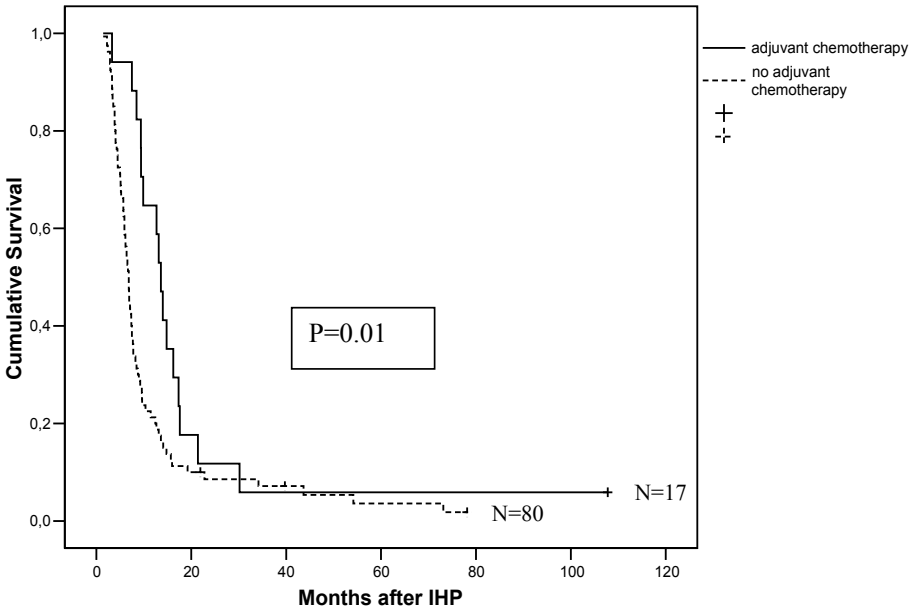

Fig 1. Progression-free survival after IHP with and without adjuvant chemotherapy. As patients were not randomized for adjuvant treatment, the difference, although remarkable could be due to selection bias.

Table 5 Multivariate Cox proportional hazards model for progression-free survival

Parameter	OR	95%CI	P
Chemotherapy directed at liver metastases prior to IHP			.30
No			
Yes	1		
	1.3	0.82 to 1.93	
Adjuvant chemotherapy			.039
No	1		
Yes	0.55	0.32 to 0.97	

patients received cytostatic treatment. Three patients underwent a combined resection and ablation of their metastases, 6 patients received ablative treatment for their liver metastases, 4 patients underwent a hepatic resection and in 1 patient lung metastases were resected. The median overall survival was 24.8 months (range 0.3 to 108 months) with an observed 3-year and 5-year survival rate of 26% and 8% respectively. Patients with a complete or partial hepatic response to IHP showed a median overall survival of 32.7 months, as compared to 16.2 months for the non-responders (P<.0001). The median survival since diagnosis of hepatic metastases was 31.8 months (range 1.83 to 110.7 months). Univariate analysis revealed a negative effect of increasing age and limited viable liver tissue, but only increasing number of metastases, absence of hepatic artery perfusion, postoperative complications and retrospective extrahepatic metastasis prior to IHP reached statistical significance (P=.01, P=.002, P=.03 and P=.008, respectively; Table 4). Risk of death by Cox proportional hazards model was 1.5 for patients of 60 years and older, 1.9 for 10 or more liver metastases, 4 for absence of hepatic artery perfusion, 1.6 for the presence of postoperative complications and 2.2 for extrahepatic metastases prior to IHP (P=.058, P=.006, P=.002, P=.048 and P=.059, respectively; Table 6).

Discussion

This study reports the results of IHP with 200 mg melphalan in 105 colorectal cancer patients. Hepatic response rate was 50% with a median progression free survival of 7.4 months and a median overall survival of 24.8 months. Although these results are promising little is known about the appropriate timing of IHP in the treatment of liver metastases of colorectal cancer patients and whether in this selected group of patients similar results could be achieved with systemic therapy alone. Recently Alexander *et al* showed IHP with melphalan to be safe and efficacious after irinotecan-based therapy [14]. In 25 patients progressive after irinotecan-based therapy the median time to progression after IHP was 5 months, while the median overall survival was 12 months. In our study 51 patients received chemotherapy prior to IHP, mainly 5FU-based monotherapy schedules, with some patients having received either irinotecan or oxaliplatin. Hepa-

Table 6 Multivariate Cox proportional hazards model for overall survival

Parameter	OR	95%CI	P
Age			.058
<60 years	1		
≥60 years	1.52	0.99 to 2.36	
No. of metastases			.006
<10	1		
≥10	1.95	1.21 to 3.12	
Estimated % of viable liver tissue			.25
≥90%	1		
<90% and >60%	1.4	0.87 to 2.26	
≤60%	1.54	0.80 to 2.94	
Perfusion technique			.003
Hepatic artery and portal vein perfusion	1		
No hepatic artery perfusion	4.15	1.68 to 10.27	
Postoperative complications			.048
No	1		
Yes	1.54	1 to 2.36	
Extrahepatic metastases prior to IHP			.059
No	1		
Yes	2.23	0.97 to 5.11	

toxicity and hepatic response rate did not differ between patients who were pretreated with chemotherapy or not, suggesting IHP is an option for both first and second line treatment of colorectal liver metastases. The past decade, as our trial was conducted, the application of liver resection has widened, by downstaging liver metastases through neoadjuvant chemotherapy, further complicating the role and timing of IHP [22]. In view of the above, different treatment algorithms seem possible, patients could first receive systemic treatment to see if downstaging is possible and receive IHP incase of treatment failure. However, patients with a poor response to chemotherapy often show a performance status unsuitable for IHP. Therefore, in a selected group of patients, IHP could also be considered first line treatment followed by liver resection if downstaging occurs. In our study, only 4 patients underwent hepatic resection after IHP, limiting the results on efficacy and toxicity, warranting further investigation.

The recent increasing success in the development of systemic treatment of colorectal cancer patients has caused a shift in interest away from regional treatment options. Nevertheless IHP, contrary to systemic treatment, has been shown to result in long-term survival with an actual 5-year survival rate of approximately 9% [12]. Although regional treatments offer the benefit of limited systemic toxicity, they are often associated with operative morbidity and even in some cases mortality. Recent studies show perioperative mortality rates around 5% in IHP [12, 13, 15]. Ideally patients should be selected who will benefit most from this procedure. Several studies have focused on the effect of age,

tumor size, number of metastases and extrahepatic disease on disease-free and overall survival after resection cryoablation and RFA [17, 23-25], while to our knowledge no such studies exist concerning IHP. Berber *et al* examined the prognostic factors after RFA in 135 colorectal cancer patients [17]. They identified number and size of liver metastases, serum CEA level as prognostic factors for overall survival in univariate analysis and tumour size in multivariate analysis. Thirty-three percent of their patients had extrahepatic disease prior to RFA, remarkably this did not effect overall survival. In our study we determined parameters that identified the patients with superior results after IHP for colorectal cancer liver metastases. We found absence of hepatic artery perfusion, postoperative complications, number of metastases, age and presence of extrahepatic disease prior to IHP as evaluated retrospectively, of prognostic significance for overall survival in univariate analysis. In multivariate analysis only the first three remained statistically significant. Although the presence of extrahepatic disease prior to IHP did not reach significance (P=.059) for overall survival in multivariate analysis, a clear trend could be observed.

Elias *et al* reported the results 506 colorectal cancer patients who underwent a laparotomy and then a resection for liver metastases [26]. Prior to laparotomy CT scan and liver ultrasonography were performed. Unsuspected metastases were discovered in 209 (41.3%) patients; extrahepatic metastases in 82 (16.2%) patients, additional liver metastases in 152 (30%) patients and both in 25 (4.9%) patients.

Patients in our study were subjected to a spiral CT scan of both abdomen and thorax prior to enrollment and CT AP. Nevertheless, similarly to the results of Elias *et al,* 34 (22%) in our study were found to have extrahepatic disease preoperatively and did not undergo IHP. Recently percutaneous IHP procedures have been developed to enable a less invasive and repeatable procedure [27, 28]. A percutaneous approach would inhibit preoperative detection of these extrahepatic metastases and could lead to the unnecessary treatment with IHP. The preoperative detection modality of colorectal metastases has been the subject of much debate [29-31]. Truant *et al* reported a prospective double-blind comparison of FDG-PET and thoracoabdominal CT scan in 53 patients with potentially resectable liver metastases from colorectal cancer [31]. The sensitivity of PET was equivalent to that of CT (both 79%), but was superior for extrahepatic abdominal sites (63% and 25% respectively). PET, on the other hand, falsely upstaged three patients. Selzner *et al* reported the results of a prospective comparison between contrast-enhanced CT scan and FDG-PET in 76 colorectal cancer patients evaluated for liver resection [29]. CT and PET provided comparable sensitivity for the detection of intrahepatic metastases. However, extrahepatic disease was missed in one third of the cases using CT (sensitivity 64%), while PET failed to detect extrahepatic lesions in only 11% of the cases (sensitivity 89%). The introduction of a standard PET scan in our pre-IHP work up would probably reduce

the number of patients undergoing unnecessary laparotomies. On the other hand both the number of false positive patients and imaging-associated costs would increase substantially. Nevertheless, to decrease both the number of patients treated with IHP with extrahepatic disease (associated with significantly reduced overall survival) and the number of unnecessary laparotomies, preoperative work up needs to be improved. Possibly a selection of patients with an increased a priori chance of extrahepatic metastases should undergo PET-scanning prior to IHP.

Yan *et al* studied the prognostic factors for progression-free survival in 135 colorectal cancer patients treated with cryoablation with or without resection [32]. Pre- and postoperative CEA, size and number of metastases were prognostic factors for progression free survival. In our study tumor load as estimated by remaining percentage of viable liver tissue and number of metastases did not influence progression-free survival. Adjuvant chemotherapy, on the other hand, did influence progression free survival in both univariate and multivariate analysis. However, this therapy was not randomized and partially given based on the personal opinion of patients respective medical oncologists. A recent meta-analysis of seven randomized controlled trials comparing resection or RFA with observation to resection or RFA with adjuvant hepatic artery chemotherapy could not detect a survival benefit for the chemotherapy group [33]. Portier *et al* reported the results of a randomized control trial of adjuvant systemic 5FU and folinic acid compared with surgery alone after resection of colorectal liver metastases[34]. In a multicenter trial 173 patients with R0 resected hepatic metastases were randomly assigned to surgery alone or to surgery followed by 6 months of systemic adjuvant chemotherapy with a 5-fluorouracil and folinic acid monthly regimen. The 5-year progression-free survival rate was 33.5% for patients in the chemotherapy group and 26.7% for the patients in the control group (P=.028). A trend towards increased overall survival for the chemotherapy group was observed, but did not reach statistical significance. Although our study was not designed to compare IHP alone to IHP with adjuvant systemic treatment the difference in disease-free survival for the 17 patients who received adjuvant treatment was remarkable. Nonetheless selection bias can not be excluded, therefore studies with adjuvant chemotherapy after IHP should be considered.

In conclusion, the results of this study are encouraging and add to the currently available data on IHP. This is the first study to identify prognostic factors in patients who are treated with IHP. More than 10 liver metastases, absence of the ability to perfuse through the hepatic artery and postoperative complications adversely influence the overall survival, while adjuvant chemotherapy improves the hepatic response and progression-free survival. An improvement of overall and disease-free survival after IHP is likely if preoperative screening is improved and adjuvant chemotherapy is administered.

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