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Isolated and Percutaneous Hepatic Perfusion for Unresectable Liver Metastases: A Systematic Review

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1. Abstract

Liver metastases may be difficultly to manage by operative or ablative therapy, and systemic chemotherapy has usually poor results. Therefore, regional therapies have been introduced, as an alternative of systemic chemotherapy. Isolated Hepatic Perfusion (IHP) is a regional therapy which allows the delivery of high doses of chemotherapeutic agents and at the same time systemic toxicity is avoided. Recently, a novel alternative to surgical IHP has been introduced, namely Percutaneous Hepatic Perfusion (PHP) which follows the principles of minimally invasive interventions. We identified 20 studies where IHP or PHP were used for unresectable liver metastases. Case-control studies resulted in conflicting results comparing IHP with systemic chemotherapy regarding overall response rates; they showed however no difference in overall survival. Overall response rates to chemotherapy delivered by IHP in the included case series appear to be of a slightly better order to that seen following the use of systemic chemotherapy. Severe complications and especially hepatotoxicity where reported, with a relatively lower morbidity in patients who underwent PHP. All in all, there is not enough good evidence that IHP is of any benefit compared to systemic chemotherapy in the treatment of unresectable hepatic metastases outside clinical trials.

2. Introduction

The liver often represents the sole site of metastasis of many tumors. To date, the optimal treatment of liver metastases is surgical treatment. For metastatic lesions that are inoperable, ablation can offer also adequate results. However, there are metastatic lesions that are not amenable to any kind of surgical or ablative therapy and do not respond to first- or second-line chemotherapy. Unresectable liver metastases are related with disappointing survival rates; for instance, 5-year survival after chemotherapy alone for metastatic colorectal liver disease remains <1% [1].

Liver has a unique anatomy, as it receives blood supply from portal vein and hepatic artery. It is also known that hepatocytes are supplied mostly from the portal vein, whereas tumor cells are supplied from hepatic artery [2]. Based to this knowledge various regional therapies targeting only tumor cells have been introduced. The concept is to introduce chemotherapeutic agents in a way to specifically target tumor cells to increase efficacy and avoid systemic toxicity, while the healthy liver tissue is sparred. Regional therapies such as Hepatic Arterial Infusion (HAI) or Trans Arterial Chemo Embolization (TACE) are used lately, with decent outcomes. On the other hand, isolated hepatic perfusion (IHP) is not used widely, although it has a theoretical advantage, as through IHP chemotherapeutic agents are delivered directly to liver tumor cells, while they do not reenter the systemic circulation. Noxious side effects to other organs are thereby minimized or avoided, allowing administration of therapeutic agents at levels that would normally cause severe systemic toxicities.

This technique was first described by Ausman in 1961 but was soon

abandoned due to high morbidity and lack of evidence supporting its efficacy [3]. Interest was renewed in the 1990's; at that time, it was conducted that hyperthermic conditions increases vascular permeability allowing increased delivery of the chemotherapeutic agents [4]. Therefore, through IHP in hypothermic conditions even higher doses of chemotherapeutic agents were delivered, resulting in dramatically better outcomes. Later an alternative method of isolated hepatic perfusion, the percutaneous hepatic perfusion was introduced. This is a minimally invasive method in which although the basic principle of IHP is followed, no surgical operation is performed as the vascular access is gained through vessel catheterization.

This systematic review evaluates the efficacy of isolated hepatic perfusion and percutaneous hepatic perfusion in terms of tumor response rate, while also examining the best possible agent and dose. It also assesses the associated morbidity and mortality.

3. Material and Methods

3.1. Search Strategy

The present systematic review was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5] (Supplemental Table 1) and in accordance with the protocol agreed by all authors. Eligible studies were identified through search of PubMed/Medline, EMBASE, and the Cochrane Library (end-of-search date March 15th, 2019). The literature search was independently performed by two reviewers (GB and KB) using Boolean operators (AND, OR, NOT) in combination with the keywords: "isolated hepatic perfusion", "IHP", "percutaneous hepatic perfusion", "PHP" or "isolated liver perfusion". Original studies, published in English, reporting tumor response rates of patients with unresectable liver disease after isolated or percutaneous liver perfusion were considered eligible for the present systematic review.

Studies were excluded if: 1) reported on non-consecutive patients, 2) reported less than 10 subjects, 3) reported pediatric population, or were 4) letters to the editor including no original data, 5) reviews, 6) animal studies, 7) abstracts, 8) non-English literature. Any disagreements were resolved by consensus with the third author (PA).

3.2. Data Collection

Two reviewers (GB and KB) extracted the data independently and any discrepancies were identified and resolved by the third author (PA). The following data were extracted: mean age, method of perfusion, chemotherapeutical agent, dosage, temperature at perfusion, tumor response rates (defined by comparing pre-treatment and post-treatment CT scans), morbidity, mortality as well as progression-free and overall survival.

3.3. Data Extraction

Data were extracted by two reviewers (KB and GB) and checked by a third (PA). Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) [6]. Complete response was considered the complete disappearance of all established tumor without evidence of new lesions. Partial response was considered a $\geq$ 30% decrease in the sum of the longest diameters of target lesions. Progressive disease was defined as $\geq$ 20% increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest diameter recorded or the appearance of one or more new lesions. Finally, as stable disease was defined the cases where neither a partial response nor a progressive disease was observed.

4. Results

4.1. Literature Search Results

The initial literature search yielded 253 potentially relevant studies. After screening titles and abstracts, 126 studies were retrieved for full-text evaluation. Ultimately, 20 studies satisfied our inclusion criteria [7-26] and a total number of 667 patients were identified (Supplemental Figure 1). Twelve studies were retrospective cohorts, one was prospective cohort, and six studies were prospective clinical trials (three phase I clinical trials and three phase II clinical trials). Finally, Rizell et al reported 2 study populations (the third one was excluded from our study); for the first study population, representing the first era of IHP, data were collected retrospectively and for the second study population, representing the second era of IHP, data were collected prospectively. There was significant heterogeneity among studies in relation to tumor types; therefore, we examined outcomes in patients with liver metastases from colorectal cancer (n = 310) and ocular melanoma (n = 199) separately.

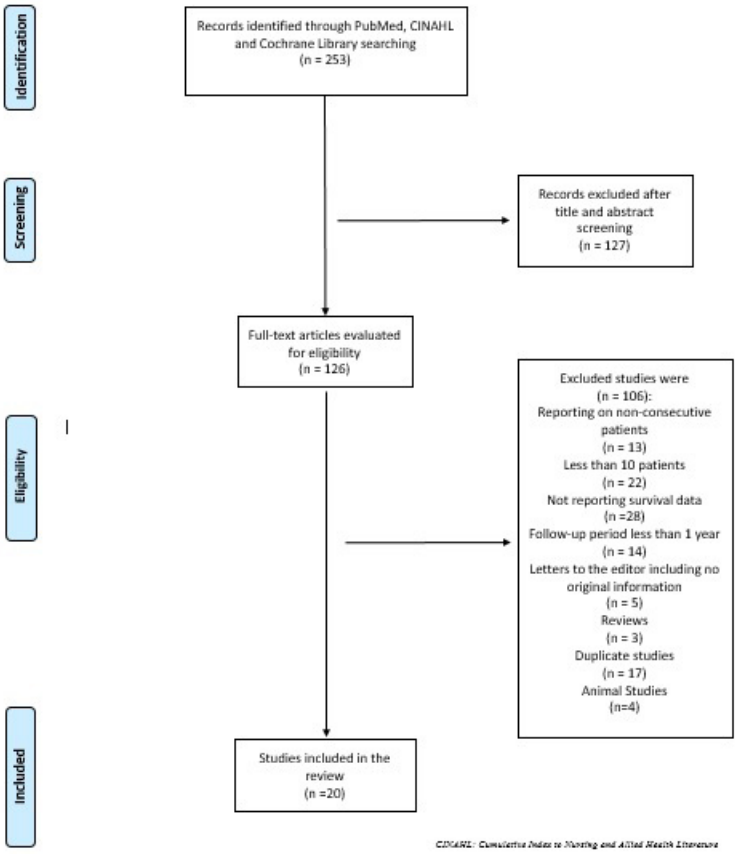
There were certain eligibility criteria for patient participation in each study which, generally, were as follow: i) patients had histologically or cytologically proven measurable liver metastases, without evidence of extrahepatic metastatic disease ii) unresectable disease was defined as multiple, usually bilobar lesions, which could not be resected without compromising postoperative liver function iii) adequate liver function. All patients were staged with standard staging procedures including computed tomography (CT) scan of the abdomen and the chest.

4.2. Technique

In most studies (n=14) an isolated hepatic perfusion was performed, while percutaneous hepatic perfusion was the preferred method in the most recent studies. In all but 2 studies, melphalan was the main agent used, although the delivered doses varied between studies (Table 1). In some studies, melphalan was given along with other chemotherapy agents, mainly oxaliplatin, but also cisplatin and TNF-α. Zeh et al [13] used only oxaliplatin, and Magge et al [17] used 5-FU and Oxaliplatin.

In studies where isolated hepatic perfusion was performed, a lap-

arotomy was initially performed and a veno- venous bypass for shunting of the inferior vena cava blood flow to the systemic circulation was established. The extracorporeal bypass incorporated a roller pump, oxygenator, heat exchanger and reservoir. Venous cannulation for establishing the extracorporeal bypass differed between studies. Then the IHP circuit was established through an inflow cannula placed mostly in proper hepatic artery; in a minority of some series, a dual perfusion, utilizing the portal vein as well (HA+PV) was used. The outflow cannula was mostly placed in retrohepatic Inferior Vena Cava (IVC). After cross-clamping of the porta hepatis and suprahepatic IVC for complete isolation of the liver the perfusion was undergone for 60 minutes in all studies (Table 1). Perfusate temperature varied from 37 ^{0}C to 41 ^{0}C. The perfusate was primed in all instances with 300 ml of packed erythrocytes.



Supplemental Figure 1: PRISMA search flow diagram

Table 1: Features and methodology in each study

Reference	No of patients	Age (mean, years)	Method	Agent	Dose	Temperature
Lindner et al 2009 [7]	11	60	IHP	Melphalan+	TNF-α: 40-200μg;	37-39 ^{o}C
				TNF-α	Melphalan:0.5mg/kg	
Alexander et al 2003 [8]	29	49	IHP	Melphalan	1.5mg/kg(90-120mg)	NR
Grover et al 2004 [9]	13	44	IHP	10 pts melphalan;	Melphalan: 100(84-	39.5-40 ^{o}C
				2 pts melphalan + TNF-α;	144);	
				1pt TNF-α	TNF-α:1mg	

Rizell et al 2008 (1) [10]	11	50	IHP	11 pts melphalan;	Melphalan: 0.25mg/kg;	41 °C
				7 pts additive cisplatinum;	TNF-α: 30μg;	
				2 pts additive TNF-α	Cisplatinum: 0.5mg/kg	
Rizell et al 2008 (2) [10]	11	56	IHP	Melphalan	2mg/kg	40 °C
Van Iersel et al 2008 [11]	18	51.4	IHP	Melphalan	200mg	39.5 °C
Alexander et al 2009 [12]	120	52	IHP	Melphalan +	Melphalan:1.5mg/kg (median:105mg);	39-40.8 °C
				TNF-α	TNF: median:1mg	
Zeh et al 2009 [13]	10	50	IHP	Oxaliplatin	5mg/m^2-60mg/m^2	40 °C
Van Iersel et al 2010 [14]	99	NR	IHP	Melphalan	200mg	39.5 °C
Varghese et al 2010 [15]	17	53	IHP	Melphalan	1,5 mg/kg	40 °C
Vogl et al 2013 [16]	14	54	PHP	hhggfj	3 mg/kg (in 1 pt 2mg/kg)	NR
			PHP	Melphalan		
Magge et al 2013 [17]	12	55.5	IHP	5FU + oxaliplatin	5-FU: 200 mg/m^2	NR
					Oxaliplatin: 40 mg/m^2	
Magge et al 2014 [18]	91	54.34	IHP	69 pts Melphalan;	Melphalan:1.5mg/kg;	40 °C
				10 pts Oxaliplatin;	Oxaliplatin: 40mg/m^2;	
				12 pts Oxaliplatin + 5FU	5FU: 200mg/m^2;	
Forster et al 2014 [19]	10	63	PHP	Melphalan	3 mg/kg	NR
Olofsson et al 2014 [20]	34	61	IHP	Melphalan	1 mg/kg	40 °C

Van Iersel et al 2014 [21]	11	57.9	IHP	Oxaliplatin + Melphalan	3 pts Oxaliplatin 50 mg + Melphalan 100mg;	39.5 °C
					4 pts Oxaliplatin 100 mg + Melphalan 100mg;	
					4 pts Oxaliplatin 150 mg + Melphalan 100mg	
Hughes et al 2016 [22]	44	55	PHP	Melphalan	3 mg/kg (2.5 mg/kg when DLT)	NR
Ben-Shabat et al 2016 [23]	68	61	IHP	62 pts Melphalan;	52 pts Melphalan 1mg/kg;	60 pts 40 °C;
				4 pts additive Cisplatin;	8 pts Melphalan 2 mg/kg;	8 pts 41 °C
				2 pts additive TNF-α	4 pts Melphalan 0.5 mg/kg + Cisplatin 0.5 mg/kg;	
					2 pts Melphalan 0.5 mg/kg + TNF-α 30 µg/kg;	
					1 pt Melphalan 0.5 mg/kg	
Kirstein et al 2017 [24]	15	NR	PHP	Melphalan	3 mg/kg	NR
Vogl et al 2017 [25]	18	55	PHP	Melphalan	3 mg/kg	NR
Abbott et al 2017 [26]	11	NR	PHP	Melphalan	NR	NR

In studies where percutaneous hepatic perfusion was undergone, 3 percutaneous catheters with sheaths were usually placed in femoral artery, in femoral vein, and in jugular vein. Systemic anticoagulation with heparin was performed in all studies. Then the chemotherapy infusion catheter was placed through the arterial sheath and advanced under fluoroscopic guidance into the proper hepatic artery distal to the takeoff of the GDA. A prophylactic coil embolization was performed in some patients to prevent retrograde flow of the chemotherapeutic drug into the GDA. Next a double-balloon hepatic isolation and aspiration was advanced through the venous sheath into the retrohepatic inferior vena cava (IVC) and was aspirated in order to occlude the hepatic part of IVC, while fenestrations in the catheter between the two occlusion balloons allowed for venous outflow from the hepatic veins to be

shunted extracorporeally and using a perfusion bypass machine the venovenous bypass was established. Then melphalan was administered through the arterial catheter at a dose of 3 mg/kg except some cases where the dose was reduced due to dose-limit-toxicity. Intra-arterial perfusion was performed for 30 minutes. In all studies, a mean number of 3 sessions were undergone.

4.3. Response Rate

The response rates of liver metastases regardless the location of primary tumor appear in Table 2. In all cohorts, partial response, as a result of the hepatic perfusion, was observed; its frequency ranged from 20% [24] up to 83.3% [9]. Complete response was observed in 11 cohorts, with its maximum frequency in the second cohort from Rizell et al [10], where complete response was noted in 25% of all treated patients. Although partial response or stable disease were the most predominant outcomes after treatment with hepatic perfusion, progressive disease was noticed in 11 cohorts totally. Finally, we did not observe significant difference in terms of response rates between patients who underwent IHP and patients who underwent PHP.

The response rates of colorectal cancer liver metastases are presented in Table 3. In all but one cohort, partial response was observed with comparable frequency between patients with colorectal liver metastases and overall. Complete response was observed again in in all but the half of cohorts, ranging from 1,6% to 11%. Likewise, progressive disease was also present in patients from 4 cohorts. Comparing the cohorts where patients with colorectal liver metastases were studied among with patients with liver metastases from other primary tumors we noticed no significant difference in response rates; the only exception was in the early study from Lindner et al [7], in which patients with colorectal liver metastases had no complete nor partial response to hepatic perfusion.

The response rates of liver metastases after uveal melanoma are presented in Table 4. Partial response was observed in all cohorts, whereas complete response was appeared in 4 cohorts reaching its maximum frequency in the cohort from Ben-Shabat et al [23]. However, progressive disease was noted in 6 out of 10 cohorts, though its frequency was relatively lower in comparison to progressive disease after treatment overall. Despite this, the frequencies of partial and complete response in patients with uveal melanoma liver metastases (in cohorts where patients with other primary tumors were evaluated) were remarkably better; in the cohort of Foster et al the overall partial response frequency was 50%, whereas 10% of patients had eventually progressive disease, while the partial response frequency in patients with uveal melanoma liver metastases was 80% and no single patient developed post-interventional progressive disease.

Table 2: Treatment outcomes, all types of primary tumors

Reference	Response rate	Grade 3 – 4 Adverse events	Follow up (months)	Mortality	Progression-free survival (months)	Overall survival (months)
Lindner et al 2009 [7]	PR: 33.3%	NR	Up to 47	2 patients (18.2%)	Median 6	Median 16
	SD: 66.7%					
Alexander et al 2003 [8]	CR: 10%,	19 patients (65%)	Median 11, up to 40	0%	Median 8	Median 12.1
	PR: 52%					
	NR 38%					
Grover et al 2004 [9]	PR: 83.3%	9 patients (69.2%)	Median 23, up to 84	1 patient (7,7%)	Median 9	Median 23
	PD: 17.7%					
Rizell et al 2008 (1) [10]	PR: 75%;	1 patient (9.1%)	Up to 41.5	3 patients (27.3%)	NR	Median 7
	SD: 25%					
Rizell et al 2008 (2) [10]	CR: 25%	1 patient (9.1%)	Up to 57	3 patients (27.3%)	NR	Median 13
	PR: 75%					
Van Iersel et al 2008 [11]	CR: 5.6%	10 patients (55,5%)	Median 74, up to 137	0%	Mean 9,6	Mean 19
	PR: 33.3%					
	SD: 50%					
	PD: 11.2%					
Alexander et al 2009 [12]	CR: 1.6%	NR	Up to 108	5 patients (4.2%)	Median 7	Median 17.4
	PR: 59%					
	NR: 39.4%					

Zeh et al 2009 [13]	PR 55%; CR: 11% SD: 22% PD: 12%	3 patients (33.3%)	Up to 48	1 patient (10%)	Median 15	Median 25
Van Iersel et al 2010 [14]	CR: 3.2%, PR: 47.3%, SD: 23.6% PD: 25.9%	37 patients (37.4%)	Up to 115	6 patients (6.1%)	Median 7.3	Median 25
Varghese et al 2010 [15]	CR: 6,.25% PR: 43.75% NR: 50%	NR	Up to 72	1 patient (5.9%)	NR	Median 11.9
Vogl et al 2013 [16]	CR: 8.3% PR: 50% SD: 41.7%	11 patients (84.6)	Up to 10	1 patient (7.1%)	NR	NR
Magge et al 2013 [17]	PR: 83.3% SD: 16.7%	5 patients (41.7%)	Median 24	0%	NR	NR
Magge et al 2014 [18]	PR + CR: 64.7%; NR: 35.3%	19 patients (20.9%)	Up to 28	3 patients (3.3%)	NR	NR
Forster et al 2014 [19]	PR: 50% SD: 40% PD: 10%	NR	Median 11.5	0%	Median 8	Median 36.3
Olofsson et al 2014 [20]	CR: 12% PR: 56% SD: 18% PD: 14%	3 patients (8.8%)	Up to 70	0%	Median 7	Median 26
Van Iersel et al 2014 [21]	PR: 33.3 % PD: 66.7%	4 patients (36.4%)	Up to 71	2 patients (18.2%)	NA	Median 18.7
Hughes et al 2016 [22]	PR: 36.4% SD 52.3% PD: 11.3%	15 patients (35.7%)	Up to 16	3 patients (4.8)	Median 5.4	Median 10.6
Ben-Shabat et al 2016 [23]	CR: 20% PR 48% SD: 20% PD: 12%	6 patients (9.5%)	Up to 96	5 patients (7.3%)	Median 10	Median 22.4
Kirstein et al 2017 [24]	PR: 20% SD: 60% PD: 20%	26 patients (89.7%)	Median 3.7	2 patients (13.3%)	NA	NA
Vogl et al 2017 [25]	PR: 44.4% SD: 38.9% PD: 16.7%	NR	Up to 41	0%	Median 12.4	Median 9,6
Abbot et al 2017 [26]	PR: 36.4% SD: 63.6%	NR	Up to 20.8	0%	Median 12	Median 20.3
NR: not reported, NA: not applicable						

Table 3: Treatment outcomes, colorectal cancer liver metastases

Reference	No of patients	Response rate	Grade 3 – 4 Adverse events rate	Follow up (months)	Mortality	Progression-free survival	Overall survival
Lindner et al 2009 [7]	5	SD: 100%	NR	Up to 47	2 (40%)	Median 6, mean 5	Median 16
Alexander et al 2009 [12]	120	CR: 1.6% PR: 59% NR: 39.4%	NR	Up to 108	5 patients (4.2%)	Median 7	Median 17.4
Zeh et al 2009 [13]	10	PR 55%; CR: 11% SD: 22% PD: 12%	3 patients (33.3%)	Up to 48	1 patient (10%)	Median 15	Median 25
Van Iersel et al 2010 [14]	99	CR: 3.2%, PR: 47.3%, SD: 23.6% PD: 25.9%	37 patients (37.4%)	Up to 115	6 patients (6.1%)	Median 7.3	Median 25
Magge et al 2013 [17]	12	PR: 83.3% SD: 16.7%	5 patients (41.7%)	Median 24	0%	NR	NR
Magge et al 2014 [18]	54	PR + CR: 68.2% NR: 31.8%	17 patients (31.5%)	Up to 28	2 patients (3.7%)	Median 12	Median 23
Van Iersel et al 2014 [21]	8	PR: 40% PD: 60%	NR	Up to 71	2 patients (3.7%)	NA	Median 13.75
Kirstein et al 2017 [24]	2	PR: 50% (1 patient) PD: 50% (1 patient)	NR	3.7	0%	NA	NA

NR: not reported**, NA:** not applicable

Table 4: Treatment outcomes, uveal melanoma liver metastases

Reference	No of patients	Response rate	Grade 3 – 4 Adverse events rate	Follow up (months)	Mortality	Progression-free survival	Overall survival
Lindner et al 2009 [7]	2	PR: 50% SD: 50%	NR	Up to 48	0%	Mean 7.5	Mean 27.5
Alexander et al 2003 [8]	29	CR: 10%, PR: 52% NR: 38%	19 patients (65%)	Median 11, up to 40	0%	Median 8	Median 12.1
Van Iersel et al 2008 [11]	12	PR: 33%, SD: 50%, PD: 17%;	NR	Median 74, up to 137	0%	Median 6.6	Median 10

Varghese et al 2010 [15]	17	CR:6,25% PR: 43.75% NR: 50%	NR	Up to 72 months	1 patient (5.9%)	NR	Median 11.9
Forster et al 2014 [19]	5	PR: 80% PD: 20%	NR	NR	0%	Median 7.6	Median 26.1
Olofsson et al 2014 [20]	34	CR: 12% PR: 56% SD: 18% PD: 14%	3 patients (8.8%)	Up to 70	0%	Median 7	Median 26
Van Iersel et al 2014 [21]	3	PR: 33.3% PD: 66.7%	NR	Up to 31	0%	NA	Median 18.7
Ben-Shabat et al 2016 [23]	68	CR: 20% PR 48% SD: 20% PD: 12%	6 patients (9.5%)	Up to 96	5 patients (7.3%)	Median 10	Median 22.4
Kirstein et al 2017 [24]	11	PR: 33.3% SD: 66.6%	NR	Median 3.7	2 patients (18.2%)	NA	NA
Vogl et al 2017 [25]	18	PR: 44.4% SD: 38.9% PD: 16.7%	NR	Up to 41	0%	Median 12.4	Median 9,6

NR: not reported**, NA:** not applicable

4.4. Toxicity and Perioperative Mortality

In order to compare the toxicity of treatment in each cohort, we categorised the adverse events according to the Common Terminology Criteria for Adverse Events [27]. The frequencies of severe adverse events (grade 3 – 4) in each cohort are found in Table 2. In studies where IHP was used, hepatic toxicity occurred in a relatively large number of patients resulting in toxicity rates ranging from 8.8% to 69.2%. As expected, newer studies reported lower rates of adverse events. In studies where PHP was used, hepatic artery spasm was the main perioperative complication, while myelosuppresion occurred frequently after the intervention, resulting in high rates of toxicity, up to 89.7%. The toxicity rate in studies where PHP was used is significantly higher compared to those where IHP was used, even compared to the early ones. When comparing the adverse events in patients with different primary tumors, no significant differences in terms of frequency are noticed (Tables 3 and 4).

Perioperative mortality rate is also appeared in Table 2. Mortality rate ranged from 0% to 27,3%; of note, in only 7 out of 21 cohorts no perioperative mortality was reported. Unlike toxicity, mortality rate is relatively lower in cohorts where PHP was performed, ranging from 0% up to 13.3%. When compared mortality rates in patients with different primary tumors (Tables 3 and 4) we observed that perioperative mortality was significantly lower among patients with uveal melanoma liver metastases, except for the cohort from Kirstein et al [24]. However, the number of patients died perioperatively was relatively low, thus no safe conclusions can be extracted.

4.5. Progression-Free Survival and Overall Survival

The median progression-free survival in each cohort appears in Table 2. Median progression-free survival varied from 5,4 to 15 months, while in the study from Kirstein et al [24] all patients who had treatment response were progress-free, in a median follow-up time of 3.7 months. There was no notable difference in terms of progression-free survival between IHP and PHP. Likewise, there was no significant difference in progression-free survival between patients with different types of tumors.

Median overall survival ranged from 7 to 36.3 months (Table 2). Again, no significant difference regarding overall survival was observed between PHP and IHP. Nonetheless, compared to the overall survival after IHP and PHP in general, overall survival in patients with colorectal or uveal melanoma liver metastases was slightly better, without reaching level of significance though (Tables 3 and 4).

5. Discussion

This study has systematically reviewed the use of isolated hepatic perfusion and percutaneous hepatic perfusion in the treatment of unresectable hepatic metastases. The main objective of IHP or PHP is to deliver higher doses of chemotherapeutic agents directly

to the liver metastases while sparing healthy liver parenchyma and minimizing systemic toxicity in patients with unresectable metastatic liver disease. Theoretically, these techniques could lead in higher tumor response rates with less systemic complications and thus better progression-free and overall survival rates.

The most commonly used chemotherapeutic agent was melphalan, either as monotherapy or in combination with other agents. Alexander et al [12] utilized TNF-α along with melphalan; yet only the latter had a significant impact on disease progression; in fact, the use of melphalan was a statistically significant factor for longer overall survival. Oxaliplatin and 5FU have been used as well. Magge et al [18] compared response rates in patients receiving a combination of melphalan and oxaliplatin and patients receiving oxaliplatin and 5FU. Response rates of combined therapy with oxaliplatin and 5FU were better, although they did not reach statistical significance. Cisplatin was also used as an additive agent by Ben- Shabat et al [23], with no clear survival benefit.

Isolated hepatic perfusion is a complex surgical procedure with considerable peri-operative morbidity; therefore, the percutaneous hepatic perfusion as a less invasive procedure was introduced. The chemotherapeutic agents used in PHP patients were not different; however, PHP patients received significantly higher doses of chemotherapeutic agents. Higher doses of chemotherapeutic agents allow lower duration of the perfusion (30 minutes' vs 60 minutes) which can also theoretically reduce hepatic injury. Given the direct application of high-dose chemotherapy to the liver through IHP or PHP, it is not surprising that the most common adverse outcome was a temporary hepatotoxicity effect. In studies where PHP was used, the hepatotoxicity was significantly lower, however most patients experienced severe yet reversible blood toxicity, which was mostly expressed as myelosuppression. Nevertheless, complications such as heart or renal failure, hepatic injury and wound infection were not found in patients who underwent PHP. Although the morbidity between IHP and PHP may vary, perioperative and postoperative mortality rates are relatively same.

To date, any patient with colorectal liver metastases which are not technically resectable receives a first-line systemic chemotherapy, which includes fluoropyrimidine (intravenous 5-FU or capecitabine), usually combined with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) [28, 29]. Additionally, the VEGF antibody, bevacizumab can also be combined with the above until disease progression or toxicity appears [30]. In fit patients, younger than 75 years the triplet combination regimen FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) is also used as first line treatment; yet the superiority of this treatment has not been sufficiently proven [31]. Cetuximab or panitumumab can be combined with a first-line chemotherapy in RAS and BRAF wild-type patients to achieve a significant increase in RR and improve patient outcome [32]. Regorafenib, an oral multikinase inhibitor, and TAS-102, an oral combination of the nucleoside analogue trifluridine and a thymidine phosphorylase inhibitor, showed a similar benefit of prolongation of OS in heavily pretreated patients with mCRC compared with BSC alone [33, 34].

Although response rates of systemic chemotherapy for metastatic colorectal cancer are considerably high (up to 50%) [19], are short lived, with duration of less than 1 year. Our study conducted that treatment with IHP and PHP achieves even higher response rates, yet without clear benefit in terms of progression-free or overall survival. Although a direct comparison would be biased due to patient selection, interesting results can be excluded from the case-control studies. Van Iersel et al [14] compared IHP with systemic chemotherapy in patients with colorectal liver metastases. They found no difference in overall response rate and no difference in overall survival. Due to the lack of comparative data, IHP and PHP methods are reserved only for patients unfit for treatment and after I-, II- or III-line treatment [28]. Currently, there is no standard treatment for metastatic uveal melanoma which is not amenable to surgery. Once metastatic disease has developed, options include observation or participation in trials, as no curative treatment has been identified yet. Trials (mostly phase II studies) examining the role of systemic treatments with regimens including dacarbazine, temozolomide, cisplatin, bendamustine, treosulfan, fotemustine-based regimens and others had poor results, with response rates generally <10%, disease control of <4 months and survival of <1 year [35, 36]. Promising data emerged though from in vitro experiments, which suggested that immunotherapy may have a role in treatment of metastatic uveal melanoma [37]. Typically, UM cells 'evade' immunoregulation by inhibiting the proliferation of T cells through the expression of specific ligands - that is, immune check- points that bind to T cell receptors. The immune checkpoint blockade genes expressed in UM include CTLA4, PD1, PDL1, TIGIT and LAG3 [38]. Therapies with immune checkpoint blockade at the level of CTLA4 [39] or PD1 [40] demonstrated however response rates of <10% and a median survival of <1 year. Additional novel immunological strategies, including adoptive T cell therapy [41] and T cell redirection [42] have also demonstrated promising preliminary results.

Our study demonstrates that IHP and PHP treatment achieves better response rates compared to those from immunotherapy or systemic chemotherapy, with limited effect on survival though. In the case control study by Hughes et al [22], the overall response rate of patients underwent PHP was statistical significantly higher than the patients who received systemic chemotherapy as best alternative care, although that did not reflect on the overall survival, except the patients who initially received BAC and after were able to cross over to PHP treatment, who had slightly better OS. Olofsson et al [20] compared the OS between patients who underwent IHP and patients who had unresectable liver metastases and were

retrieved by national registry data. Although it is a rough comparison, they managed to show a statistically significant difference regarding OS. Therefore, IHP and PHP should be considered for patients with metastatic uveal melanoma, in the setting of a clinical trial [43].

There are a number of limitations to this study. The level of evidence currently available is poor, as our results were mostly retrieved from case-series studies. The case-control study of Van Iersel [14] does not include a randomized arm and clinically relevant differences may exist between the two populations assessed. Moreover, most series have used melphalan for IHP or PHP and the use of other chemotherapeutic agents may demonstrate a different response and complication profile. Lastly, the number of studies regarding IHP/PHP published is relatively low, for establishing a level of evidence. Further studies should be conducted, to acquire more experience on the subject.

6. Conclusions

It is well known that systemic chemotherapy has poor results in cases of unresectable liver metastases, therefore the need of alternative therapies is high. Isolated hepatic perfusion and its conservative alternative, percutaneous hepatic perfusion seems to have some benefit over classic chemotherapy in terms of tumor response. Unfortunately, this is not translated to statistically significant better overall survival. To justify the complications associated with this procedure a significant improvement in complete tumor response and patient survival should be demonstrated. It seems that there is no actual difference between IHP and PHP outcomes regarding response rates and overall survival. Of interest, PHP was the method of choice in the only case control study that showed statistical significance regarding better response rates. In terms of perioperative and postoperative morbidity, PHP seems to have a slight advantage over IHP. Nevertheless, there is not enough good evidence and further studies and especially case control studies or studies comparing IHP, and systemic chemotherapy should be conducted.

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