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ONCOLOGY

Percutaneous hepatic perfusion (chemosaturation) with melphalan in patients with intrahepatic cholangiocarcinoma: European multicentre study on safety, short-term effects and survival

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Abstract

Objectives Cholangiocarcinoma is the second most common primary liver tumour with a poor overall prognosis. Percutaneous hepatic perfusion (PHP) is a directed therapy for primary and secondary liver malignancies, and its efficacy and safety have been shown in different entities. The purpose of this study was to prove the safety and efficacy of PHP in patients with unresectable intrahepatic cholangiocarcinoma (iCCA).

Patients and methods We retrospectively reviewed data from 15 patients with unresectable iCCA treated with PHP in nine different hospitals throughout Europe. Overall response rates (ORR) were assessed according to response evaluation criteria in solid tumours (RECIST1.1). Overall survival (OS), progression-free survival (PFS) and hepatic PFS (hPFS) were analysed using the Kaplan-Meier estimation. Adverse events (AEs) and toxicity were evaluated.

Results Fifteen patients were treated with 26 PHPs. ORR was 20%, disease control was achieved in 53% after the first PHP. Median OS was 26.9 months from initial diagnosis and 7.6 months from first PHP. Median PFS and hPFS were 122 and 131 days, respectively. Patients with liver-only disease had a significantly longer median OS compared to patients with locoregional lymph node metastases (12.9 vs. 4.8 months, respectively; $p < 0.01$). Haematological toxicity was common, but manageable. No AEs of grade 3 or 4 occurred during the procedures.

Discussion PHP is a standardised and safe procedure that provides promising response rates and survival data in patients with iCCA, especially in non-metastatic disease.

Key Points

- *Percutaneous hepatic perfusion (PHP) offers an additional locoregional therapy strategy for the treatment of unresectable primary or secondary intrahepatic malignancies.*
- *PHP is a standardised and safe procedure that provides promising response rates and survival data in patients with intrahepatic cholangiocarcinoma (iCCA), especially in non-metastatic disease.*
- *Side effects seem to be tolerable and comparable to other systemic or local treatment strategies.*

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Keywords Percutaneous hepatic perfusion · Cholangiocarcinoma · Liver neoplasms · Chemosaturation

Abbreviations

ACT	Activated clotting time
AE	Adverse events
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BAC	Best alternative care
CCA	Cholangiocarcinoma
iCCA	Intrahepatic cholangiocarcinoma
CR	Complete response
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ECOG	Eastern Cooperative Oncology Group
G-CSF	Granulocyte-colony stimulating factor
HAI	Hepatic arterial infusion
HCC	Hepatocellular carcinoma
HGB	Haemoglobin
INR	International normalized ratio
LFT	Liver function test
MRI	Magnetic resonance imaging
OM	Ocular melanoma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
hPFS	Hepatic progression-free survival
PHP	Percutaneous hepatic perfusion
PLT	Platelet count
PR	Partial response
RECIST	Response evaluation criteria in solid tumours
RFA	Radiofrequency ablation
SD	Stable disease
TACE	Transarterial chemoembolisation
TARE	Transarterial radioembolisation
ULN	Upper limit of normal

Introduction

Cholangiocarcinoma (CCA) is the second most common primary liver tumour with increasing incident rates between 2.1 and 3.3 per 100,000 [1]. Whereas perihilar and distal disease represent about 90%, intrahepatic CCA (iCCA) occurs in less than 10% of patients [2].

Surgical resection is so far the only curative option for non-metastatic iCCA, with a median survival time of 36 months and 3-year survival rates of 40–60% for R0 resection. However, this can only be achieved in less than 30% of patients with iCCA [2]. Furthermore, recurrence rates are high even in cases of R0 resection. In a metastatic and locally advanced unresectable situation palliative chemotherapy with gemcitabine and cisplatin represents the standard of care [3]. For patients with unresectable tumours without extrahepatic spread, locoregional therapies may be used similar to hepatocellular carcinoma (HCC) therapy. Options in this realm include radiofrequency ablation (RFA) for patients with few yet well-defined lesions with a diameter up to 5 cm [4, 5], and both transarterial chemoembolisation (TACE) [6–8] and transarterial radioembolisation (TARE) [9, 10] for patients with larger or diffuse tumours. Studies on locoregional therapies are mostly retrospective and single-centre with various results.

Percutaneous hepatic perfusion (PHP) offers a new locoregional therapy strategy for the treatment of unresectable primary or secondary intrahepatic malignancies. Efficacy has been shown in a randomised phase 3 trial in patients with liver metastases of ocular or cutaneous melanoma with prolonged progression-free survival (PFS) and improved hepatic objective response compared to best alternative care (BAC) [11]. A single-centre study recently showed the safety of the procedure and demonstrated promising outcome results in patients with different tumours. Another study presented data from ocular melanoma patients with comparable results [12, 13]. However, very few data exist regarding the use of PHP in a patient cohort of iCCC.

The aim of this retrospective, multicentre study was to analyse the safety and efficacy of PHP in 15 patients with unresectable iCCA as last-line therapy.

Patients and methods

From June 2012 to August 2016 15 patients with histologically proven iCCA at nine different hospitals throughout Europe were selected for PHP treatment as last-line therapy by the respective local multidisciplinary tumour board in each centre. Data were collected and evaluated locally, anonymised and submitted for retrospective evaluation.

It should be noted that three patients were already included in the evaluation of another retrospective study on safety and efficacy of PHP including 29 patients with different primary and secondary liver malignancies [12].

This retrospective study was approved by our institutional review board.

Patient selection

Only patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, with

adequate haematological, renal and hepatic function (haemoglobin > 8 g/dl; leukocyte count > 2,000/μl; platelets > 50,000/μl, serum creatinine < 60 μmol/L, bilirubin ≤ 3 × upper limit of normal (ULN)) were included. Four patients had locoregional lymph node metastases. Distant extrahepatic metastases, recent history of transient ischaemic attacks, heart failure (left ventricular ejection fraction < 40%) or significant chronic obstructive or restrictive pulmonary disorder were considered contraindications for PHP. All but one patient underwent standard treatment for CCA including surgery, if applicable, and systemic chemotherapy.

Data acquisition

Anonymised patient data included prior tumour therapies, ECOG status, baseline tumour load, laboratory data and outcome data. Toxicity and peri-interventional complications were reported using the common terminology criteria for adverse events (CTCAE v4.03) and taking peri- and post-interventional laboratory reports into account.

Treatment outcome was measured according to the response evaluation criteria in solid tumours (RECIST 1.1) [14]. Therefore, either computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3 months after PHP. Overall survival (OS) was calculated from initial diagnosis and first PHP until last follow-up or death. Progression-free survival (PFS) was analysed from first PHP until first radiological intra- or extrahepatic progression, last follow-up or death, whichever occurred first; hepatic progression-free survival (hPFS) was calculated in the same way but only for intrahepatic progression.

Procedure

All patients were planned for one PHP with the option of re-treatment in case of stable disease (SD) or partial response (PR) according to the RECIST 1.1 criteria. In case of complete response (CR) or progressive disease (PD) patients did not receive an additional PHP.

For PHP a dedicated delivery and filter system (CHEMOSAT® second generation, Delcath Systems Inc.) was used (Fig. 1). A catheter, inserted through the femoral artery into the hepatic artery, is used for arterial chemoperfusion of the liver with a dosage of 3.0 mg/kg ideal body weight up to a maximum dose of 220 mg of melphalan (Fig. 2a). A double-balloon catheter, inserted through the femoral vein, facilitates isolation of the hepatic inferior caval vein segment (Fig. 2c). Venous blood from the liver, extracted through side holes of the double-balloon catheter, is filtrated via an extracorporeal haemofiltration circuit. A sheath in the internal jugular vein is used for blood return. During the infusion phase, 500 cc of melphalan solution is administered in aliquots of 100 cc at a rate of 0.4 ml/s with an angiogram in between to check the flow in the hepatic artery. Subsequently washout is performed with the filtration circuit running for 30 min. In order to maintain an activated clotting time (ACT) above 500 s, which is mandatory for safe extracorporal haemofiltration, heparin is administered as needed.

All procedures were performed under general anaesthesia due to the length of the procedure and haemodynamic changes that occur with the extracorporeal haemofiltration circuit and inferior caval vein occlusion [11, 15].

Statistical analysis

Statistical analyses were performed using JMP Pro 13.0 (SAS Institute Inc., Cary, NC, USA).

Survival, including subgroup analysis, was assessed using the Kaplan-Meier estimation. Differences were calculated using the log rank test. Continuous data were tested for significance using the Mann-Whitney *U* test. Level of significance was set to 0.05.

Results

Patient and procedure characteristics

In 15 patients with histologically proven iCCA a total of 26 PHP procedures (range 1–5) were performed. The median procedure time was 177.5 min with a median melphalan dose of 188 mg. An overview on patients' and procedure characteristics is shown in Table 1. A detailed summary of each patient is reported in Table 2.

Therapy response

After the first PHP one patient (7%) presented with CR, two patients (13%) had PR, and SD was observed in eight patients (53%). Three patients (20%) presented with PD and one patient died before follow-up imaging at 46 days after PHP treatment due to sepsis and liver failure. The patient with CR was not treated again and is still alive. Five of the patients with SD received a second treatment resulting in PR (20%) and PD (20%) in one patient and SD in three patients (60%). Subsequently third, fourth and fifth treatments were performed in two patients with SD during long-term follow-up (Fig. 3). Tumour response is summarised in Table 2. Median time between first diagnosis and first PHP was 17.2 months (range 2.0–41.5 months); median time between first and second PHP was 3.2 months (range 2.1–4.2 months).

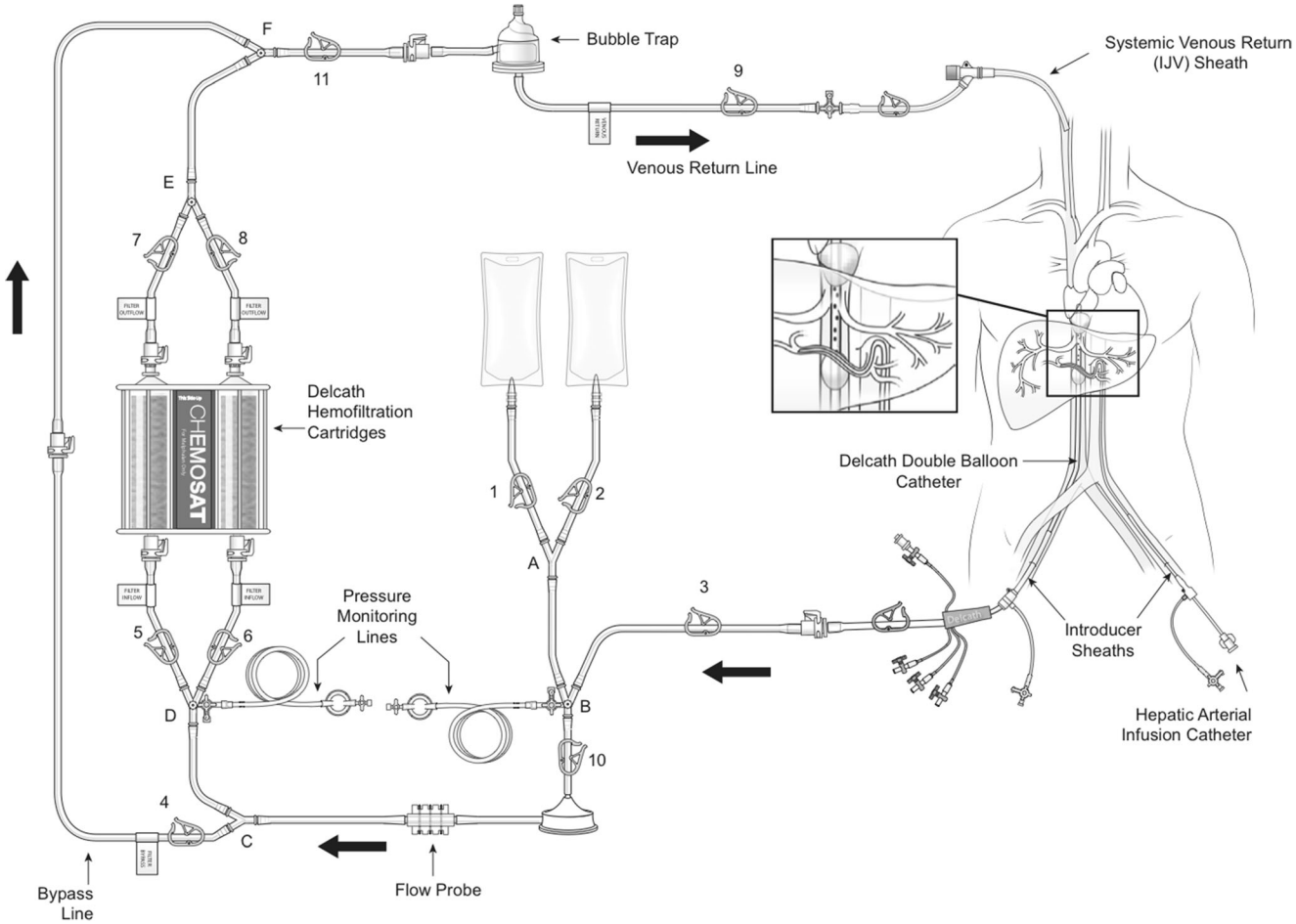

Fig. 1 Percutaneous hepatic perfusion (PHP) setup (CHEMOSAT®, Delcath Systems Inc., New York, NY, USA) with closed circuit of catheters and filters for arterial chemoperfusion, venous filtration and venous blood return using a veno-venous bypass

Survival

Median OS was 26.9 months from initial diagnosis and 7.6 months from first PHP (n = 15). One-year OS rate from first PHP was 40%. Median PFS was 122 days; median hPFS was 131 days, respectively. Kaplan-Meier curves for OS and PFS are shown in Fig. 4. At the time of data analysis in August 2017 two patients were still alive; one patient is lost to follow-up.

In a subgroup analysis patients with locoregional lymph node metastases were compared to patients with liver only disease. Median OS from first PHP was significantly shorter in patients with locoregional lymph node metastases (4.8 months)

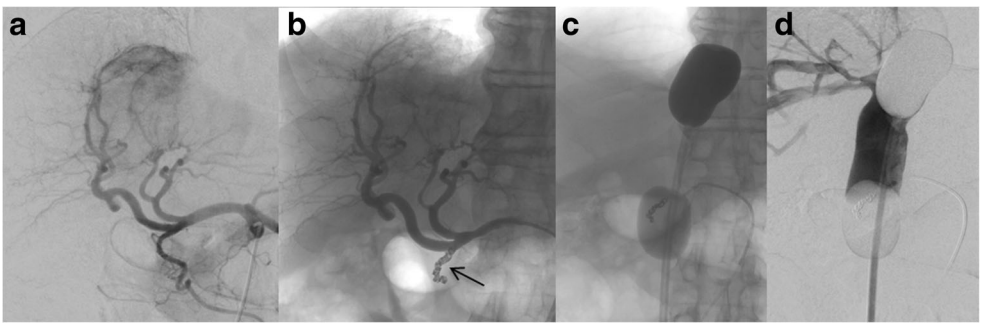

Fig. 2 Percutaneous hepatic perfusion (PHP) procedure: Initial DSA angiogram of the celiac trunk (**a**); angiogram with catheter in treatment position in the common hepatic artery (**b**), note that the gastroduodenal artery is sealed by means of the coil embolisation (arrow); balloon positioning for isolation of the hepatic segment of the inferior caval vein (**c**), proper sealing is confirmed by retrograde venogram (**d**)

Table 1 Patient and procedure characteristics

Characteristic	
Patient population (n) (gender)	15 (8 male/7 female)
Age (y)*	59 (51–62)
BMI (m^2/kg)*	26.1 (21.3–28.4)
Karnofsky-Index (%)*	90 (85–100)
ECOG performance status	
0	12 (80%)
1	3 (20%)
Tumour burden (%)*	20 (15–35)
Time first diagnosis to first PHP (m)*	17.2 (7.5–24.3)
Prior therapy (n)	
Systemic chemotherapy	14 (93%)
Transarterial therapy	3 (20%)
Hepatic resection	1 (7%)
Microwave ablation	1 (7%)
Stereotactic radiation therapy	1 (7%)
No prior therapy	1 (7%)
Procedure time (min)	177.5 (151.5–192)
Melphalan dose (mg)	188 (167–220)

*Data are median (interquartile range)

compared to patients without (12.9 months, $p < 0.01$). Median OS from initial diagnosis was 27.0 months for patients with liver-only disease and 18.5 months for patients with locoregional lymph node metastases, respectively, showing a comparable strong trend close to reaching statistical significance ($p = 0.052$).

Complications

There were no AEs of grades 3 or 4 during the PHP procedure. Hypotension and tachycardia were common during the time of haemofiltration but could be adequately treated by use of volume replacement and catecholamine administration, and were self-limiting at the end of the procedure.

Post-procedural complications included pneumonia in four patients after one treatment each, which were treated with antibiotics. In one patient a stroke with a temporary mild hemiparesis occurred, which resolved spontaneously without any neurological deficits over a time period of 2 months. One patient showed a relevant groin haematoma at the puncture site without need for transfusion. Another patient developed a common femoral artery pseudoaneurysm in the left groin, which was surgically treated. Acute renal failure occurred in one patient, which caused a prolonged hospital stay. Dialysis was not necessary and renal function was normal at the time of hospital discharge. The patient with the highest tumour load in the liver (40%) developed acute multi-organ failure shortly after the treatment and despite intensive care treatment this patient died without tumour progression 46 days after PHP.

Post-procedural AEs of grades 3 to 5 are summarised in Table 3.

Toxicity

To evaluate toxicity of the PHP procedure haematological, hepatic and biliary function were assessed immediately before and 1 day after treatment for all treatments. Follow-up data were also available for days 5–7 (n = 21/26) and for days 21–45 (n = 13/26) after the PHP. Results of the blood tests and significance levels are shown in Table 4.

A substantial decrease of haemoglobin (HGB, $p < 0.0001$) and platelet count (PLT, $p < 0.0001$) was observed early after PHP. This resulted in the need for erythrocyte concentrate transfusion in seven patients and platelet concentrate transfusion in six patients, respectively. After 21–45 days, median HGB returned to near baseline and median PLT values were increased compared to baseline. No relevant changes in the leukocyte count were present 1 day after PHP. After 5–7 days WBC dropped significantly. Granulocyte-colony stimulating factor (G-CSF) was administered in four patients with leucopenia. After 30–45 days WBC returned to near baseline values before PHP.

In direct relation to the PHP procedure, only minor changes in liver function tests (LFTs) could be observed with mildly elevated aspartate aminotransferase (AST) 1 day after the procedure and a mild increase in ALT and total bilirubin on days 5–7; in contrast a significant decrease in serum level of alkaline phosphatase (ALP) was shown after 1 day.

The INR (International Normalized Ratio) was significantly increased on the day after the procedure compared to the day before and returned to near baseline as early as 5–7 days after PHP. In addition, we noticed a significant increase in C-reactive protein (CRP) as a marker of inflammation ($p < 0.01$) immediately after PHP, which remained elevated at 5–7 days post PHP and returned to baseline at follow-up.

Discussion

PHP is a relatively new technique offering a minimally invasive liver-directed treatment of primary and secondary liver malignancies.

In our multi-institutional study, we observed an overall response rate (ORR) of 20% and disease control in 53% of patients after first PHP. Median PFS and hPFS were 122 and 131 days, respectively; median OS was 26.9 months from initial diagnosis and 7.6 months from first PHP. These results were achieved after considerable pretreatment with a median time from initial diagnosis to first PHP of 17.2 months and in all but 1 patient with progressive disease under systemic therapy. With this in mind, the results support the promising perspective of PHP in iCCA patients. The benefit is especially

Table 2 Detailed patient and procedure characteristics, therapy response and clinical outcome

Patient	Centre	Sex	Age at first PHP (years)	Prior therapy	ECOG performance status	Tumour burden (%)	Number of PHP treatments	Mean procedure time (min)	Mean melphalan dose (mg)	First response (RECIST)	Best response (RECIST)	Status	Overall survival from first diagnosis (month)	Overall survival from first PHP (month)
1	A	M	75	CTx	0	15	5	171	220	SD	SD	AWD	67.0	32.2
2	A	M	60	CTx	0	10	5	161	196	SD	SD	LFU	45.8	18.6
3	A	M	59	CTx	0	20	1	198	220	PD	PD	DOD	20.5	7.6
4	B	F	45	CTx, RTx	0	5	1	280	189	CR	CR	AWD	65.8	45.7
5	C	M	56	CTx, TACE	0	20	1	153	220	SD	SD	DOD	16.1	6.0
6	C	F	55	CTx	1	40	1	165	179	n/a	n/a	DOD	5.3	1.5
7	C	F	38	CTx	0	35	2	143	162.5	SD	SD	DOD	26.8	19.3
8	D	M	59	CTx, Sx, MWA	0	10	1	205	176	SD	SD	DOD	47.2	5.7
9	E	F	60	CTx, TACE	1	40	1	155	171	PR	PR	DOD	28.7	7.4
10	F	F	65	CTx	0	15	2	185	167	SD	SD	DOD	43.7	39.8
11	G	M	59	CTx, TACE	1	34	1	175	160	PD	PD	DOD	23.1	10.7
12	G	F	51	CTx	0	20	1	155	116	SD	SD	DOD	20.8	3.6
13	H	F	68	-	0	40	2	208	168	SD	PR	DOD	15.0	12.9
14	I	M	42	CTx	0	30	1	185	n/a	PR	PR	DOD	25.0	6.7
15	I	M	62	CTx	0	13	1	195	n/a	PD	PD	DOD	27.0	2.7

CTx chemotherapy, *RTx* radiotherapy, *TACE* transarterial chemoembolisation, *Sx* surgery, *MWA* microwave ablation, *PHP* percutaneous hepatic perfusion, *n/a* not applicable/available, *SD* stable disease, *PD* progressive disease, *CR* complete response, *PR* partial response, *AWD* alive with disease, *LFU* lost to follow-up, *DOD* dead of disease

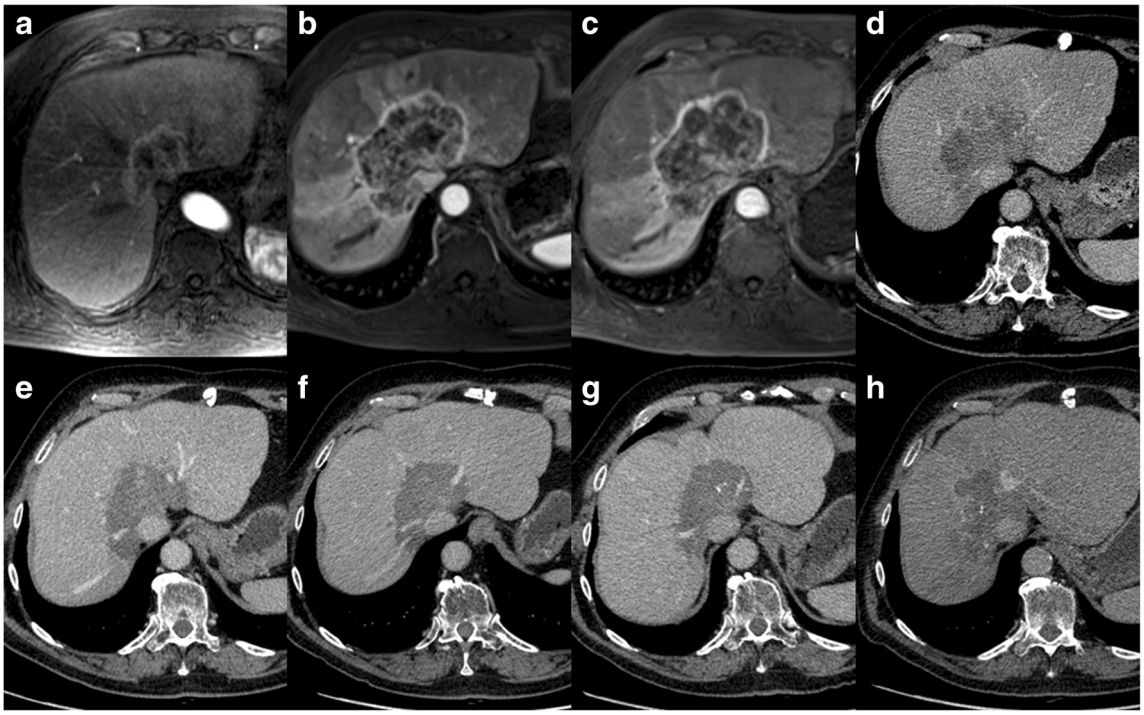

Fig. 3 A 76-year-old male patient with intrahepatic cholangiocarcinoma. MRI at the time of first diagnosis showing an intrahepatic tumour with peripheral enhancement (**a**). Progressive disease after 34 months of conventional chemotherapy (**b**). MRI after first percutaneous hepatic perfusion (PHP) (**c**) and CT after second (**d**), third (**e**) and fourth (**f**) treatment showing partial response (tumour shrinkage and reduction of contrast enhancement). As CT images after fifth PHP (**g**) showed tumour progression, the therapy regimen was changed to radioembolisation with good initial response (**h**). The patient is scheduled for further follow-up

noteworthy when considering the results of standard systemic chemotherapy with gemcitabine/cisplatin (ABC-02 trial, median OS of 11.7 months) [3, 16].

Compared to other transarterial therapies in iCCA patients, the median OS of 26.9 achieved in our study supports the results by Boehm et al with a median OS of 22.8 for HAI, which was clearly better in comparison to TARE and TACE with an OS of 13.9 and 12.4 months, respectively [17]. In another meta-analysis of TACE treatment in patients with iCCA an OS of 15.7 months from initial diagnosis and 13.4 months from first treatment was reported [18, 19], whereas a pooled analysis of TARE treatment showed an OS of 15.5 months [20], both inferior to the results of PHP and HAI.

In the subgroup analysis comparing patients with and without locoregional lymph node metastases, a significantly longer median OS from first PHP for patients with liver-only disease could be demonstrated and a strong trend was observed regarding median OS from initial diagnosis. This suggests that patients with liver-only disease may benefit even more from therapy with PHP.

The PHP procedure itself can be considered standardised and safe, as no AEs of grades 3 or 4 occurred during the procedure. We noted one patient with a minor stroke with mild hemiparesis, which was fully reversible after 2 months, possibly due to the haemodynamic changes during the procedure. The patient with the highest tumour load (40% of liver volume) and impaired liver function in our cohort experienced severe hepatic complications with a prolonged hospital stay, and died due to liver and kidney failure 46 days after the procedure. This supports the notion that tumour load and liver function are important, if not the most important, predictors for fatal complications. In agreement with other studies [11, 12] we suggest that patients with a tumour volume higher than 50% of the total liver volume and normal liver function should be excluded from PHP. In patients with abnormal liver function this threshold might even be lower. In patients with normal liver function at baseline, however, LFTs were only mildly elevated without evidence of momentous liver toxicity (Table 4).

In the present study we observed a significant haematological toxicity expressed by anaemia and thrombocytopenia the day after the PHP procedure, both improving after 5–7 days. Hence this is most likely a side effect of dilution and the extracorporeal filter system [21]. The significant increase in INR within the first week is probably a side effect of the heparin administration necessary during haemofiltration [22, 23] as it returned to near baseline as early as 5–7 days after PHP. WBC remained stable on day 1 after PHP. As shown by a single-centre study on PHP [12], we observed leukocytopenia 5–7days after PHP. This is most likely caused by melphalan-induced bone marrow suppression. In four inpatients G-CSF was administered. However, the haematological toxicities in

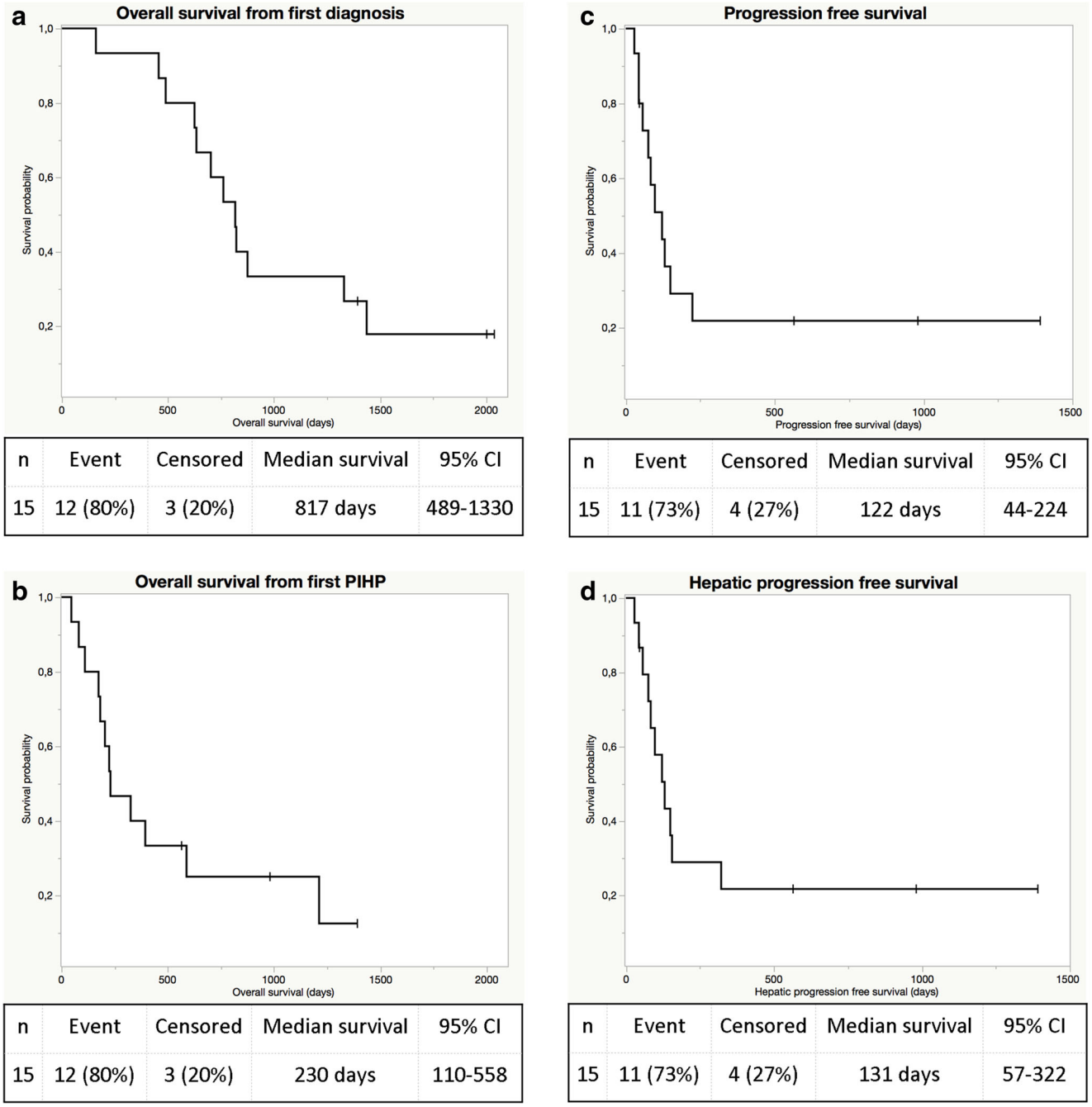

Fig. 4 Kaplan-Meier curves for overall survival from time of first diagnosis (**a**) and first percutaneous hepatic perfusion (PHP) (**b**), respectively. Kaplan-Meier curves for progression-free survival (**c**) and hepatic progression-free survival (**d**)

our study are in line with those reported in the ABC-02 trial [16], the landmark trial for systemic chemotherapy for CCA.

Based on the ABC-2 trial, systemic chemotherapy with gemcitabine plus cisplatin has become the reference regimen for advanced biliary tract cancers [16, 24]. Currently there is no evidence for second-line chemotherapy and immunotherapy. Given the heterogeneous molecular profiles in biliary cancer, targeted therapies might eventually lead to more individualised and specific treatment in the future [25]. However, the role of interventional oncology procedures in the management of ICC is increasingly being investigated [19, 20] in order to achieve higher cytotoxic concentrations in the liver. In a systematic review and meta-analysis by Boehm and co-workers, hepatic arterial infusion (HAI) therapy offered the best outcomes in terms of tumour response and survival when compared to TACE and TARE, but may be limited by toxicity [19, 20].

The main benefit of PHP over HAI is the ability to filter the cytotoxic substance, resulting in higher local and lower systemic doses [26].

Table 3 Post-procedural toxicity and complications regarding adverse events of grades 3–5 up to 45 days after percutaneous hepatic perfusion (PHP)

Adverse events	n = 26
Haematological toxicity	
Anaemia with need of transfusion	7 (27%)
Thrombocytopenia with need for transfusion	6 (23%)
Leucopenia with need for G-CSF administration	4 (15%)
Any haematological toxicity	9 (35%)
Non-haematological complications	
Pneumonia	4 (15%)
Acute renal failure	1 (4%)
Ascites	1 (4%)
Bleeding	1 (4%)
Oedema	1 (4%)
Multi-organ failure/death	1 (4%)
Otitis	1 (4%)
Pseudoaneurysm	1 (4%)
Stroke	1 (4%)
Any non-haematological complications	9 (35%)
Any adverse event of grades 3–5	13 (50%)

PHP therapy is established in patients with unresectable liver metastases from ocular or cutaneous melanoma based on one prospective randomised trial demonstrating promising tumour response and survival rates [11]. Other studies showed feasibility in patients with liver metastases from colorectal cancer and sarcoma [11–13, 27–29]. One study showed prolonged hPFS in melanoma and sarcoma patients in comparison to TARE and TACE [29]. A prospective, randomised controlled trial for patients with hepatobiliary cancer [30, 31] is currently beeing evaluated and another prospective, randomised controlled trial for patients with liver metastases of OM [32] is still recruiting.

Experience with PHP in patients with iCCA is still rather limited, with one phase 1 trial including 11 patients with hepatobiliary tumour not differentiating between CCA and HCC [26], and one multicentre study including one patient with CCA [33]. Kirstein et al demonstrated long-lasting stable disease in ten patients with hepatobiliary tumours (CCA n = 5, HCC n = 5) undergoing PHP including three patients from this study [12].

There are several limitations of this study: First, laboratory tests after discharge are only available in 50% of the procedures. Therefore, haematological long-term complications due to melphalan toxicity cannot be reliably assessed in this study. However, we have laboratory results for up to 7 days for the majority of treatments (n = 21/26). Based on results from other studies, this should be sufficient to assess melphalan toxicity [12, 33]. Still, complications may have been underestimated in our particular cohort of patients with iCCA. Second, a small number of patients were included in our study and the number of patients per centre was also small. Since the PHP procedure is highly standardised, however, the procedural and periprocedural results should be comparable between centres. Third, we performed a subgroup analysis that included node-positive patients. However, the number of patients in the subgroup was small and they had a higher median hepatic tumour load (30% vs. 15%, $p = 0.11$). This limits the value of the subgroup analysis. Nevertheless, in the absence of valid prospective data and given that iCCA is a relatively rare disease, we consider the limitations acceptable for a pilot trial that provides both short-term safety and survival data. A prospective multicentre trial is under way in order to overcome these limitations [34].

In conclusion, our study provides promising response rates and survival data in patients with advanced stage iCCA,

Table 4 Course of haematological and hepatic functions

Laboratory value	Before PHP (n = 26/26)	After PHP (n = 26/26)	Days 5–7 (n = 21/26)	Days 21–45 (n = 13/26)
HGB (g/dL)	12.2 (11.3–13.0)	9.5 (8.8–10.2)**	9.0 (8.0–10.4)*	10.8 (8.7–12.4)
PLT ($x10^9$/L)	144 (112–223)	61 (48–103)**	50 (39–132)*	175 (104–251)
WBC ($x10^9$/L)	7.1 (6.4–7.8)	7.0 (5.4–8.8)	4.3 (2.2–7.2)*	5.8 (4.3–8.0)
INR	1.09 (1.02–1.20)	1.22 (1.15–1.28)**	1.20 (1.10–1.42)	1.13 (1.07–1.30)
ALT (IU/L)	22.0 (13.5–31.5)	31.0 (14.5–54.8)	32.0 (18.0–49.0)*	25.0 (13.2–80.0)
AST (IU/L)	37.0 (29.5–54.0)	46.5 (28.5–100.2)*	38.0 (28.0–85.0)	32.0 (20.0–84.0)
GGT (IU/L)	305 (128–494)	236 (88–328)	283 (124–480)	233 (120–629)
ALP (IU/L)	169 (105–258)	112 (75–213)*	238 (177–314)	146 (100–314)
T Bil (mg/dL)	0.56 (0.41–0.82)	0.68 (0.40–1.52)	1.1 (0.81–1.58)*	1.29 (0.58–3.7)
CRP (mg/L)	11.1 (4.0–30.3)	40.0 (19.0–75.0)*	60.1 (40.1–94.6)*	15.0 (5.0–53.8)

Data are median (interquartile range)

PHP percutaneous hepatic perfusion, *HGB* haemoglobin, *PLT* platelet count, *WBC* leucocyte count, *INR* international normalized ratio, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma glutamyl transferase, *ALP* alkaline phosphatase, *T Bil* total bilirubin, *CRP* C-reactive protein

* $p < 0.05$, ** $p < 0.0001$

especially in liver-dominant disease without lymph node involvement. Side effects, although potentially under-reported, seem to be tolerable and comparable to other systemic or local treatment strategies. A randomised, controlled study comparing systemic chemotherapy with gemcitabine/cisplatin to PHP with melphalan with an estimated number of 295 patients with iCCA is anticipated to start recruiting soon [34].

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Frank K. Wacker.

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After data collection of the current study, Hannover Medical School participated in the Phase 2 Clinical Trials in Hepatocellular Carcinoma (HCC) and Intrahepatic Cholangiocarcinoma (ICC) (NCT 02415036).

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Only three of the patients were included in a retrospective single-centre study: "Safety and efficacy of chemosaturation in patients with primary and secondary liver tumors", published in *Journal of Research and Clinical Oncology*, including 29 patients with different primary and secondary liver malignancies.

In our current study only patients with intrahepatic cholangiocarcinoma across nine different hospitals in Europe were included.

Methodology

- Retrospective
- Diagnostic/prognostic study
- Multicentre study

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