

ORIGINAL RESEARCH ARTICLES

Hepatic chemosaturation with melphalan in patients with primary or secondary liver tumors with or without extrahepatic tumor manifestation

R. Veelken^{1,2†}, S. Ebel^{2,3†}, A. Schindler^{1,2}, F. Lordick^{4,5}, M. F. Struck⁶, C. Girbardt⁷, F. Ziemssen⁷, D. Seehofer^{2,8}, T. Denecke^{2,3}, T. Berg^{1,2} & F. van Bömmel^{1,2*}

¹Division of Hepatology, Department of Medicine II, University Hospital of Leipzig, Leipzig; ²University Liver Tumor Center (ULTC), University Hospital of Leipzig, Leipzig; ³Department of Diagnostic and Interventional Radiology, University Hospital of Leipzig, Leipzig; ⁴University Cancer Center Leipzig (UCCL), Leipzig; ⁵Division of Oncology, Department of Medicine II, Leipzig University Medical Center, Leipzig; Departments of ⁶Anesthesiology and Intensive Care Medicine; ⁷Ophthalmology; ⁸Hepatobiliary Surgery and Visceral Transplantation, University Hospital of Leipzig, Leipzig, Germany

Available online 22 August 2024

Background: Hepatic chemosaturation by isolated percutaneous liver perfusion (CS-PHP) with melphalan controls hepatic tumor growth. However, optimal treatment frequency and the prognostic relevance of extrahepatic tumor manifestation remain unclear. We analyzed response and tolerability of repeated treatment in regular cycles of CS-PHP. **Materials and methods:** CS-PHP was administered to patients with primary or secondary liver tumors. Overall survival (OS) and hepatic disease control rate (hDCR) were assessed retrospectively by modified RECIST after at least one response assessment, and toxicity by Common Terminology Criteria for Adverse Events v4.03.

Results: A total of 97 CS-PHP treatments were carried out in 33 patients between 2016 and 2023. Patients had unresectable intrahepatic metastases of uveal melanoma ($n = 19$), intrahepatic cholangiocarcinoma ($n = 8$), hepatocellular carcinoma ($n = 2$), ciliary body melanoma ($n = 1$), acinar cell carcinoma ($n = 1$), pancreatic cancer ($n = 1$) or tonsil cancer ($n = 1$). CS-PHP was carried out seven times in 1 patient, six times in 5, five times in 3, four times in 2, three times in 4, twice in 7 and once in 11 patients. The median OS was 65 weeks (standard error 13.6, 95% confidence interval 38.2-91.5 weeks). hDCR was 91% (30 of 33 patients) at last observation time point. Extrahepatic tumor manifestations were not associated with OS. CS-PHP was well tolerated. Grade III or IV pancytopenia occurred in two patients.

Conclusion: CS-PHP induced hepatic disease control in the majority of patients. Extrahepatic tumor manifestation had no significant impact on OS. The relevance of CS-PHP as long-term treatment needs to be validated in future studies.

Key words: liver tumor, uveal melanoma, chemosaturation, melphalan, experimental treatment, tebentafusp

INTRODUCTION

In patients with primary or secondary hepatic malignancies, treatment strategies to control intrahepatic tumor growth and spread include surgery, locoregional or systemic therapies.¹⁻³ The rates of success of these strategies depend on the liver tumor burden as well as on liver function and individual treatment tolerability.⁴ Chemosaturation (CS; CHEMOSAT®, Delcath Systems Inc., Wilmington, DE), or percutaneous hepatic perfusion (CS-PHP) with melphalan, represents a novel regional therapy strategy to treat unresectable primary or secondary intrahepatic malignancies. In

the phase III FOCUS trial, a recent single-arm, multicenter trial conducted across 40 centers in the European Union and the United States in patients with hepatic metastatic uveal melanoma (UM), the objective response rate (ORR) to treatment with CS-PHP was as high as 36.3%.⁵ The results of this trial were the basis for the Food and Drug Administration (FDA) approval for CS-PHP as treatment for adult patients with metastatic UM.

In addition to its efficacy in treating hepatic metastatic UM, CS-PHP has demonstrated activity in numerous patients with various other primary or secondary hepatic tumors.⁶⁻¹⁶ The treatment with CS-PHP was described to be well tolerated in most patients. However, the lack of a defined repetition frequency for CS-PHP and the lack of experience with its use in patients with extrahepatic tumor manifestations represent major uncertainties regarding the role of this treatment in multimodal treatment strategies. Aiming to fill this gap in knowledge, our study reports the experience with a fixed treatment regimen of CS-PHP in real-world patients

*Correspondence to: Prof. Florian van Bömmel, Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany. Tel: +41-0-341-9712330; Fax: +41-0-341-9712339

E-mail: florian.vanboemmel@medizin.uni-leipzig.de (F. van Bömmel).

†These authors contributed equally.

2949-8198/© 2024 The Authors. Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

with various primary or secondary liver tumors and aims to investigate the benefit of control of the liver tumor in patients with extrahepatic tumor manifestations.

MATERIALS AND METHODS

Patient selection

With the approval by the institutional review board (no. 264/18-ek), all patients treated with CS-PHP at our center between January 2016 and October 2023 were retrospectively enrolled.

Treatment with CS-PHP was initiated based on the decision of the institutional multidisciplinary liver tumor board in cooperation with other site-specific tumor boards. Prerequisites for CS-PHP treatment were staging imaging by either magnetic resonance imaging or computed tomography not older than 8 weeks, sufficient hematologic, renal and hepatic function, tumor burden of <50% of the liver volume and written informed consent of the patients. CS-PHP treatment was chosen for patients with dominant intrahepatic tumor spread and non-prognostic extrahepatic manifestations that were asymptomatic. CS-PHP was not offered to patients with pre-existing conditions such as liver cirrhosis, heart failure, chronic pulmonary disorders or if they had shown intolerance to a previous CS-PHP treatment (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmogo.2024.100082>). The study was carried out in accordance with the Declaration of Helsinki. Data were retrieved from hospital information system and institutional database for this specific procedure.

Treatment procedures

All patients underwent angiographic evaluation of the hepatic arteries up to 14 days before CS-PHP. Significant arterial hepato-gastric or hepato-enteric anastomoses (e.g. right gastric artery) were embolized to prevent systemic exposure to melphalan.

Patients received CS-PHP using the Hepatic CHEMOSAT® Delivery System (Delcath Systems, Inc.) according to the manufacturer's recommendations.^{8,17} Thus, CS-PHP was carried out under general anesthesia and with systemic anticoagulation. The right common femoral artery was accessed using a 4-French (F) angiography sheath, the right internal jugular vein with a 6-F sheath and the right common femoral vein using an 18-F sheath. A 4-F catheter was placed in the common hepatic artery (if there were no anatomical variants), and then a micro-catheter was placed into the intended vessel to administer melphalan, based on the CS-PHP evaluation results. A 16-F double-balloon catheter was positioned with its tip in the right atrium. The venous catheter was then connected to an extracorporeal filtration system. After all lines were in place, systemic anticoagulation (heparin 300 IU/kg) was applied until an activated clotting time (ACT) of <400 s was maintained to prevent clotting of the filter. Once the intended ACT was reached, the cranial balloon of the double-balloon catheter was inflated inside the right atrium and retracted into the

inferior vena cava, and subsequently the caudal balloon was inflated inside the inferior vena cava, directly below the orifice of the hepatic veins to prevent a systemic hepato-venous drain. Correct positioning of the two balloons was confirmed by a venous angiogram. Melphalan was administered at a dose of 3.0 mg/kg ideal body weight (maximum 220 mg/cycle) into the hepatic artery over a time frame of 0.6 ml/s. The hepatic venous blood was aspirated through the double-balloon catheter, filtered extracorporeally and returned through the internal jugular vein. The filtration was carried out during and until 30 min after the administration of melphalan.

Data collection and endpoints

All data were collected retrospectively using clinical, imaging and laboratory reports. Endpoints of our study were overall survival (OS), hepatic disease control rate (hDCR) and hepatic progression-free survival time (hPFS) during the observation time, which included at least one CS-PHP treatment and one follow-up imaging for response assessment. Adverse events (AEs) associated with CS-PHP assessed according to the Common Terminology Criteria for Adverse Events v4.03 were another endpoint.

Statistical analysis and definition of response

All variables were expressed as median (range) depending on the distribution. hDCR and hPFS were assessed according to the modified RECIST (mRECIST).^{20,21} Best response was taken as investigator-assessed response. hDCR indicates the best response achieved from the initiation of CS-PHP until cessation and was defined as the percentage of patients achieving hepatic complete response (hCR), hepatic partial response (hPR) or hepatic stable disease (hSD) after first CS-PHP until the end of treatment. hPFS was defined as time measured from first CS-PHP to hepatic tumor progression. OS was defined as time from first CS-PHP to death. Median OS and median hPFS were analyzed using Kaplan—Meier estimation. Graphs were generated with GraphPad Prism 8.0 (GraphPad Software, San Diego, CA) and SPSS 24.0 (SPSS Inc., Chicago, IL). The graphical abstract was designed using BioRender.

Response evaluation and treatment repetition

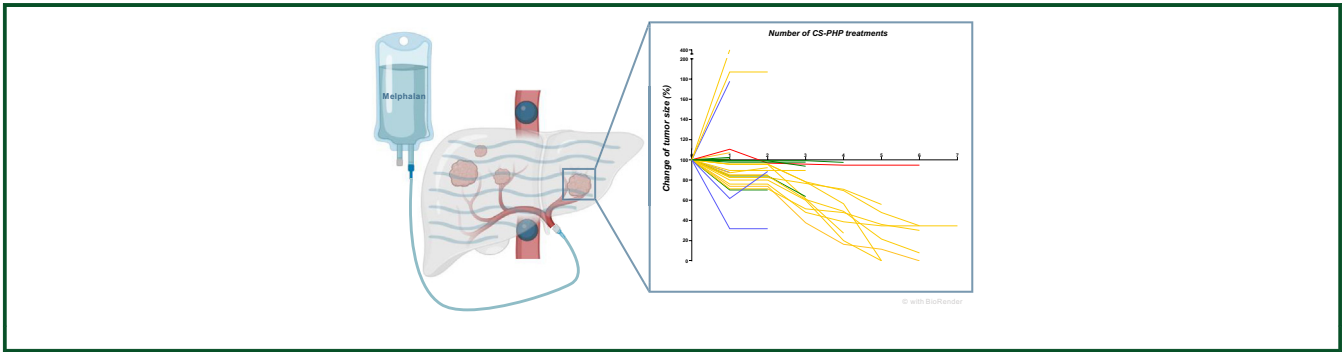
Images were assessed by two experienced radiologists and response evaluation was retrospectively verified for this study. Tumor extension before and after treatment with CS-PHP was measured based on mRECIST.^{20,21} A further course of CS-PHP was planned every 6-8 weeks if intrahepatic SD or PR was found and treatment was well tolerated. Intervals could be adjusted due to side-effects or organizational issues.

RESULTS

Patient characteristics

Thirty-three patients [23 (69.7%) female, median age 61 years (range 26-81 years)] were treated with CS-PHP 97 times (median 2, range 1-7 treatments per patient) between January 2016 and October 2023 (Table 1). Nine

GRAPHICAL ABSTRACT



patients had liver surgery and eight patients received systemic therapy before the first CS-PHP treatment. Patients had either unresectable intrahepatic metastases of UM ($n = 19$), intrahepatic cholangiocarcinoma (ICC, $n = 8$) or hepatocellular carcinoma (HCC, $n = 2$), or hepatic metastases originating from other primary cancers, including ciliary body melanoma, acinar cell carcinoma of the head/neck region, pancreatic carcinoma and tonsil carcinoma in one case each collectively referred to as ‘other’ ($n = 4$).

Before the first CS-PHP treatment, seven patients had tumor manifestations spread beyond the liver. Thus, extrahepatic tumor manifestations were present in lymph nodes ($n = 2$), multiple bones ($n = 1$) or kidney ($n = 1$). Three patients each had lung, bone and lymphatic metastases. During CS-PHP treatment, another 10 patients developed extrahepatic tumor progression, whereas the remaining 16 patients had no tumor spread beyond the liver.

Frequency of CS-PHP treatments

In total, 97 CS-PHP treatments were carried out in 33 patients with a maximum of 7 treatments per patient (Figure 1). If patients showed radiological response after CS-PHP

treatment, a consecutive CS-PHP was carried out. The interval between two CS-PHP treatments was between 6 and 12 weeks in 85% of patients and ranged up to 56 weeks in individual cases. CS-PHP was not repeated if intrahepatic tumors showed progression or complete response. CS-PHP was carried out seven times in 1 patient, six times in 5, five times in 3, four times in two, three times in 4, twice in 7, and once in 11 patients. Patients with hepatic UM or ICC received 1-7 and 1-4 CS-PHP treatments, respectively. The two patients suffering from HCC received 1 and 6 CS-PHP treatments. Patients with other metastatic entities underwent 1-2 CS-PHP sessions.

Survival in patients with or without extrahepatic tumor spread

The median OS since the first CS-PHP treatment was 65 weeks [standard error (SE) 13.6, 95% confidence interval (CI) 38.2-91.5 weeks] (Figure 2A). Patients with UM had a median OS of 69 weeks (SE 6.9, 95% CI 55.6-82.9 weeks) and patients with ICC had a median OS of 38 weeks (SE 2.9, 95% CI 32.0-43.7 weeks). At the time of analysis, 11 of 33 patients were still alive, with 6 of them actively undergoing CS-PHP treatment.

Upon the initiation of CS-PHP, 26 patients exhibited no extrahepatic tumor besides the primary cancer, while 7 patients had extrahepatic metastases (UM = 5, other = 2). Interestingly, there were no discernible differences in median OS between patients with or without extrahepatic tumor manifestations at baseline (log-rank chi-square: 1.755, $P = 0.185$) (Figure 2B).

A total of 17 patients developed extrahepatic tumor manifestation. In three of these patients, CS-PHP was continued as the hepatic disease was still controlled and the extrahepatic tumor was not considered life-limiting in view of the hepatic tumor load.

Treatment response and reasons for treatment withdrawal

The DCR of hepatic tumors was 91%, including 6 patients with hCR (18.2%), 12 patients with hPR (36.4%) and 12 with hSD (36.4%). Median hPFS was 52 weeks (SE 13.9, 95% CI 24.7-79.2 weeks) for all patients. Patients with hepatic UM

Table 1. Patient baseline characteristics	
Parameters	Value, n (%)
Patients	33 (100)
Men	10 (30.3)
Women	23 (69.7)
Age at first treatment in years; median (range)	61 (26-81)
Interval between diagnosis of primary tumor and first CS-PHP in months; median (range)	30 (0-193)
Patients with extrahepatic metastases	7 (21.2)
Intrahepatic cholangiocarcinoma	8 (24.2)
Extrahepatic metastases	0 (0)
Hepatocellular carcinoma	2 (6.1)
Extrahepatic metastases	0 (0)
Others	4 (12.1)
Extrahepatic metastases	2 (6.1)
Liver surgery before first CS-PHP	9 (27.27)
Systemic treatment before first CS-PHP	8 (24.3)
One systemic therapy	4 (12.12)
Two systemic therapies	3 (9.1)
Three systemic therapies	1 (3.0)

CS-PHP, chemosaturation with percutaneous hepatic perfusion.

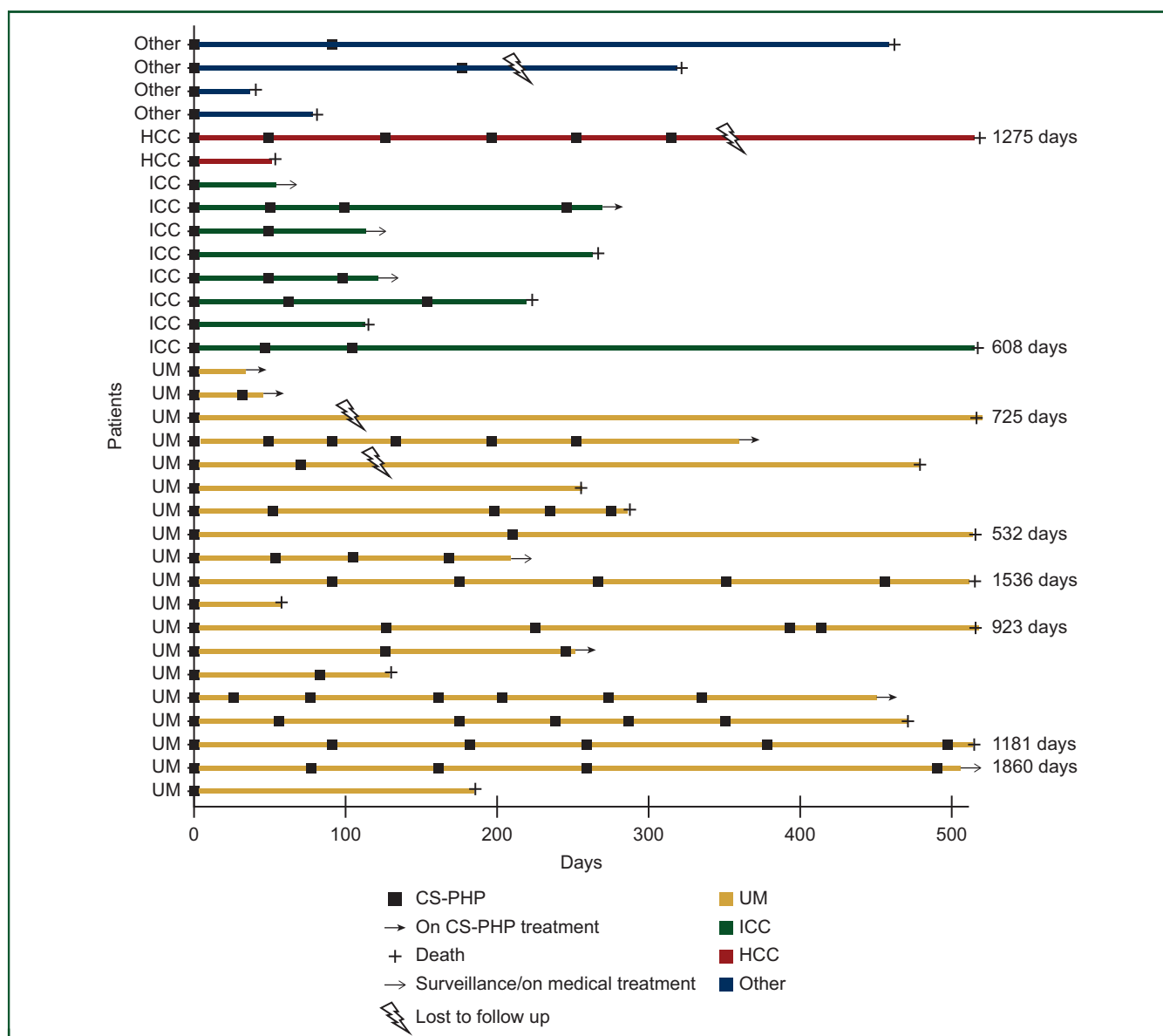


Figure 1. Individual repetitions of 97 CS-PHP treatments and survival status. CS-PHP treatments are symbolized by a square. Arrows indicate ongoing observation. Patients with a cross have died during the observation period ($n = 22$).

CS-PHP, chemosaturization with percutaneous hepatic perfusion; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocellular carcinoma; other, ciliary body melanoma, angiosarcoma, tonsil and pancreatic carcinoma; UM, uveal melanoma.

showed a median hPFS of 69 weeks (SE 15.4, 95% CI 39.1–99.5 weeks), while ICC patients showed a median hPFS of 38 weeks (SE 2.9, 95% CI 32–43.7 weeks).

Three patients (9.1%) showed no response to CS-PHP but rapid intrahepatic tumor progression (Supplementary Table S2, available at <https://doi.org/10.1016/j.esmogo.2024.100082>). This included two patients with UM and one with pancreatic cancer (Figure 3A and B). In six patients, hCR was achieved after a median of 5 (range 2–7) CS-PHP cycles.

Accordingly, CS-PHP was abandoned as a treatment due to hepatic disease progression in three patients, due to intolerability in two patients and due to loss to follow-up in four patients. The presence of extrahepatic tumor manifestation before the start of CS-PHP treatment was not associated with response of the hepatic tumor.

CS-PHP induced significant tumor shrinkage in individual patients, as for example demonstrated in a 28-year-old female with multiple hepatic UM metastases with a diameter of up to 10 cm. After six CS-PHP treatment sessions over a period of 9 months, the patient achieved hCR (Figure 4A). In another patient with ICC, an individual treatment decision for CS-PHP as first-line therapy was made because of rapid intrahepatic tumor progression and after four CS-PHP cycles hPR was achieved after 11 months (Figure 4B).

Safety and tolerability of CS-PHP

A total of eight AEs occurred during or shortly after the intervention, including tissue edema, hematoma, bleeding and renal failure, all of which were resolved and were

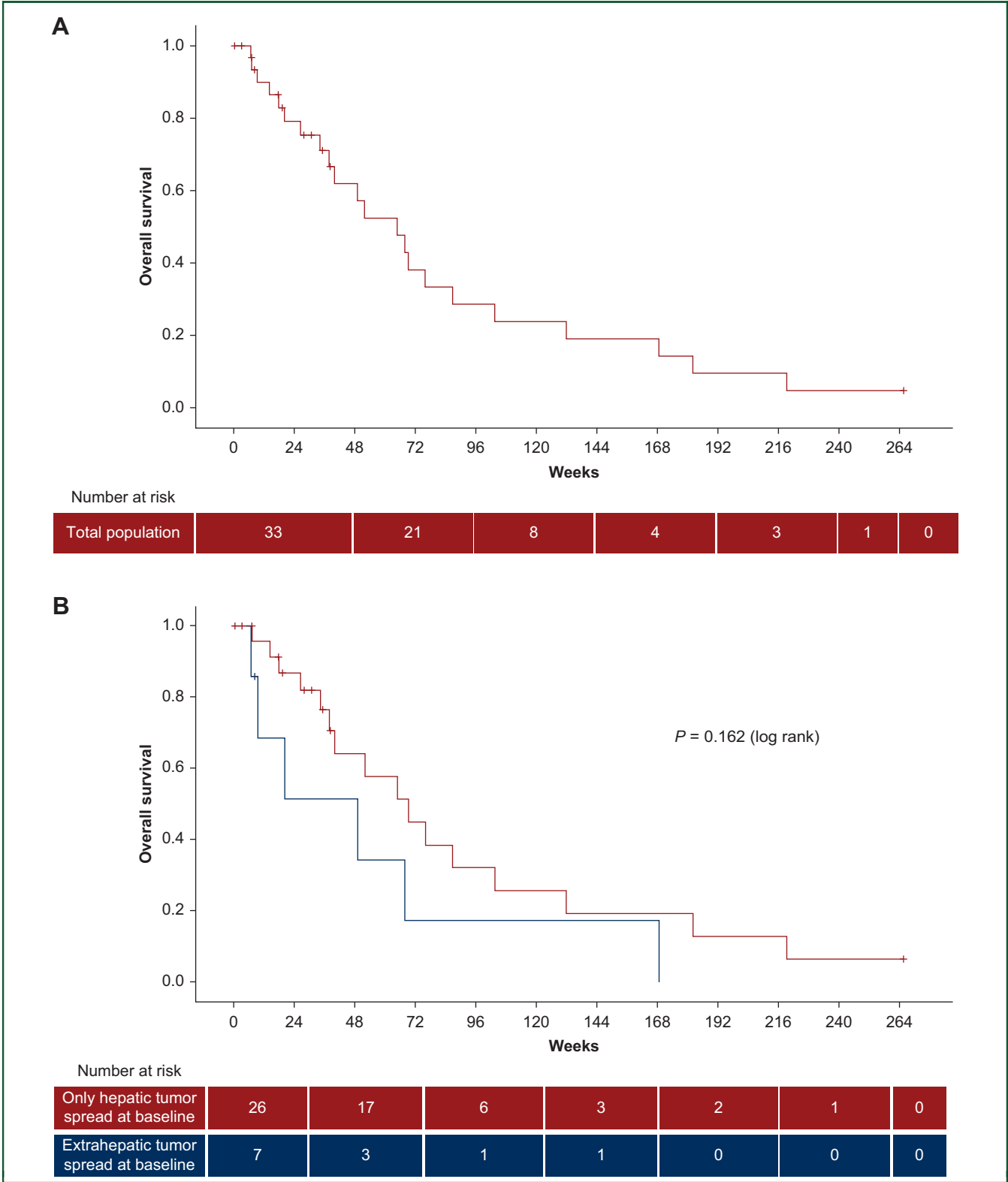


Figure 2. Overall survival during CS-PHP of the total population. (A) Kaplan–Meier estimates of survival during CS-PHP in the total population. (B) Kaplan–Meier estimates of survival during CS-PHP according to extrahepatic tumor spread at the start of treatment. CS-PHP, chemosaturation with percutaneous hepatic perfusion.

summarized in a different publication.²² After CS-PHP, patients were admitted to intensive care, with most being transferred to normal ward the next day. Almost all patients experienced laboratory changes matching grade AE definitions. Most grade I-II AEs were hematologic,

such as leukopenia, neutropenia, thrombocytopenia and anemia. Liver necro-inflammation and function showed transient increases in bilirubin and alanine aminotransferase levels but normalized by day 35, indicating no significant liver damage even after multiple CS-PHP

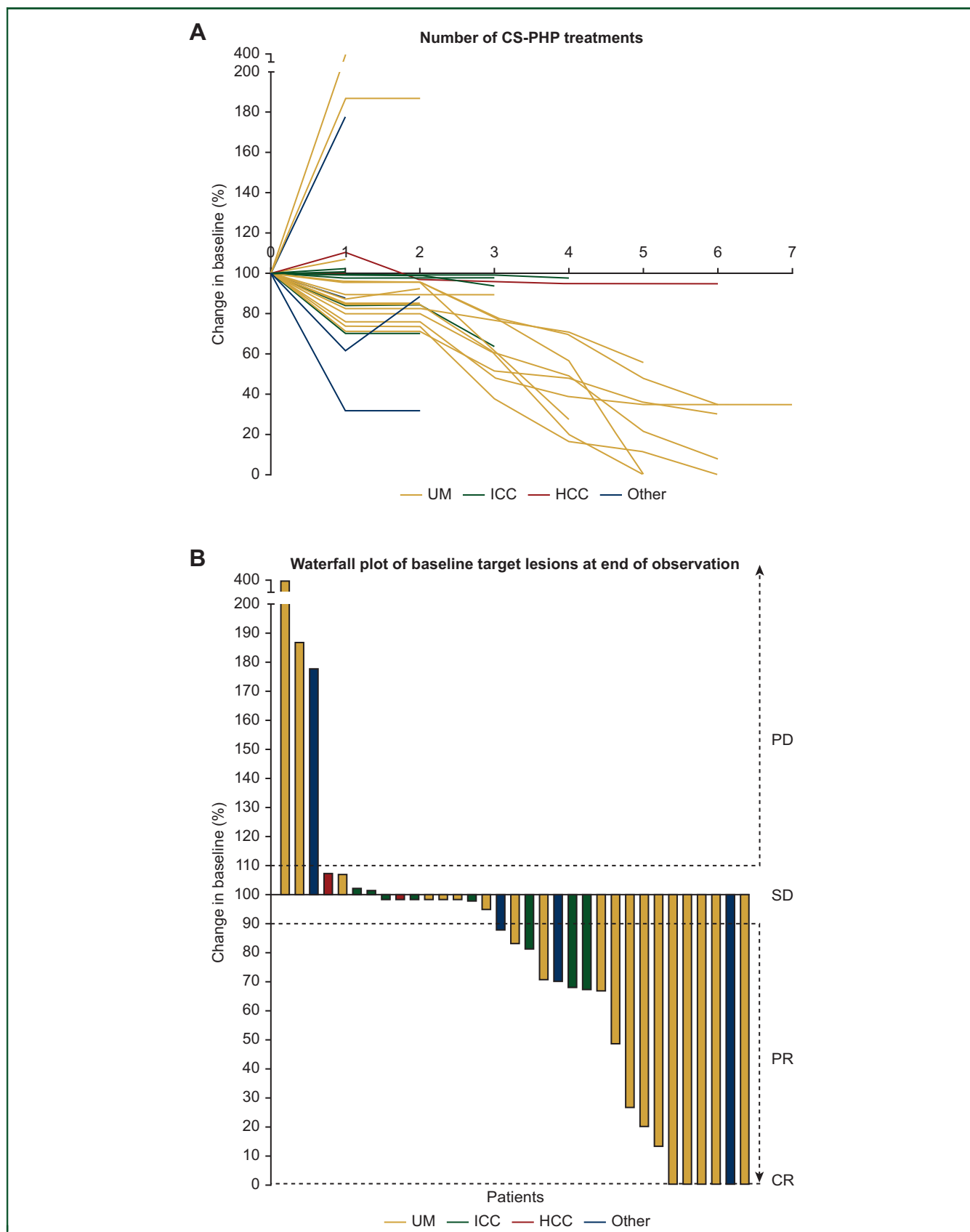


Figure 3. Individual changes in tumor sizes during CS-PHP treatment. (A) Individual changes in tumor sizes during CS-PHP treatment. On the y-axis the change in tumor size is indicated according to the baseline lesions. (B) Waterfall plot of changes in the size of target lesions at the end of observation. Dashed lines are thresholds for hepatic PD, hepatic SD, hepatic PR and hepatic CR. CR, complete response; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocellular carcinoma; other, ciliary body melanoma, angiosarcoma, tonsil and pancreatic carcinoma; PD, progressive disease; PR, partial response; SD, stable disease; UM, uveal melanoma.

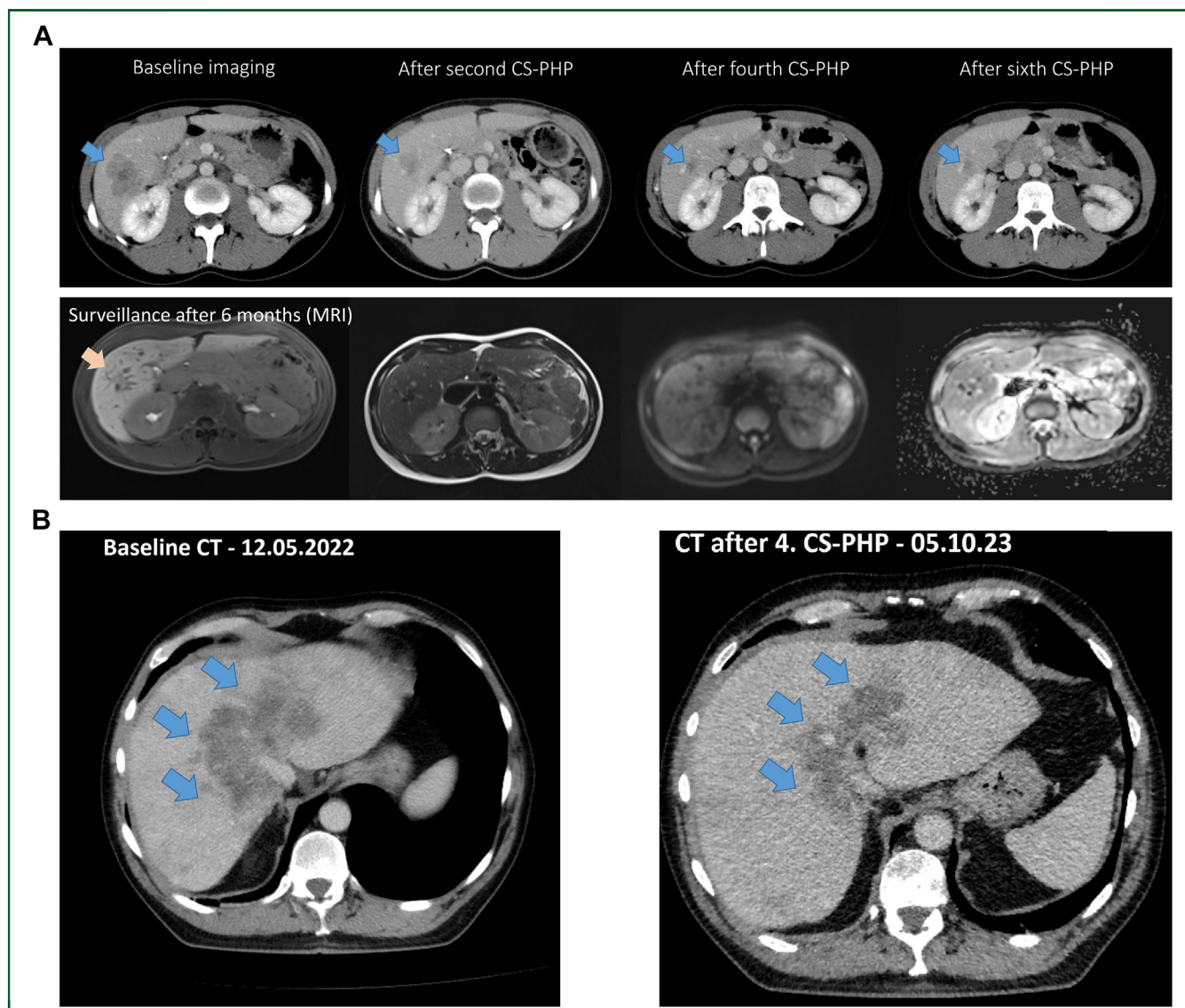


Figure 4. Example for response of UM liver metastasis to repeated CS-PHP treatment. (A) Example for response of UM liver metastasis to repeated CS-PHP treatment. At the start of CS-PHP treatment, a large liver metastasis in liver segment 5/8 (blue arrow) showed hCR after six CS-PHP treatments within 9 months. Surveillance imaging after 6 months after the last CS-PHP showed no remaining tumor. Top row: Contrast-enhanced CT in the portal venous phase at the level of the upper abdomen shows shrinkage of the tumor. Bottom row: Contrast-enhanced MRI 6 months after the sixth CS-PHP shows no tumor with suspected residual scar (orange arrow) in the area of the former metastasis. Left to right: T1 post-contrast in the hepatobiliary phase, T2 HASTE, diffusion-weighted imaging, ADC map. (B) Example for local control of central liver metastasis of ICC (blue arrows). Contrast-enhanced CT in the portal venous phase at the level of the upper abdomen. On the left, a large, unresectable ICC surrounding the hepatic veins and the inferior vena cava can be seen. On the right, CT image after four sessions of CS-PHP shows shrinkage of the tumor with residual vital tumor.

ADC, apparent diffusion coefficient; CT, computed tomography; CS-PHP, chemosaturation with percutaneous hepatic perfusion; HASTE, half-Fourier acquisition single-shot turbo spin-echo; ICC, intrahepatic cholangiocellular carcinoma; MRI, magnetic resonance imaging; UM, uveal melanoma.

treatments (Figure 5A and B). Two ICC patients developed persistent grade III-IV pancytopenia, and one patient had severe leukocytopenia and thrombocytopenia due to bone marrow infiltration of UM. CS-PHP was discontinued in two patients due to complications (takotsubo cardiomyopathy or non-catheterizable splenic artery) and in two others due to unspecified discomfort at their own will.

Follow-up and causes of death

CS-PHP was primarily used as a last-line therapy, with follow-up treatments tailored to each patient. Twenty-

two patients died during follow-up. Three (two with UM and one with pancreatic cancer) did not respond to CS-PHP and died from intrahepatic tumor progression (Figure 1). One ICC patient treated with ivosidenib after CS-PHP did not achieve disease control. Ten patients with intrahepatic disease control from CS-PHP experienced dominant extrahepatic progression, leading to CS-PHP cessation.

For three of these patients, individual therapies were attempted. One UM patient received ipilimumab and nivolumab for bone and lung metastases, later one, as genetic analysis became standard of care, therapy was

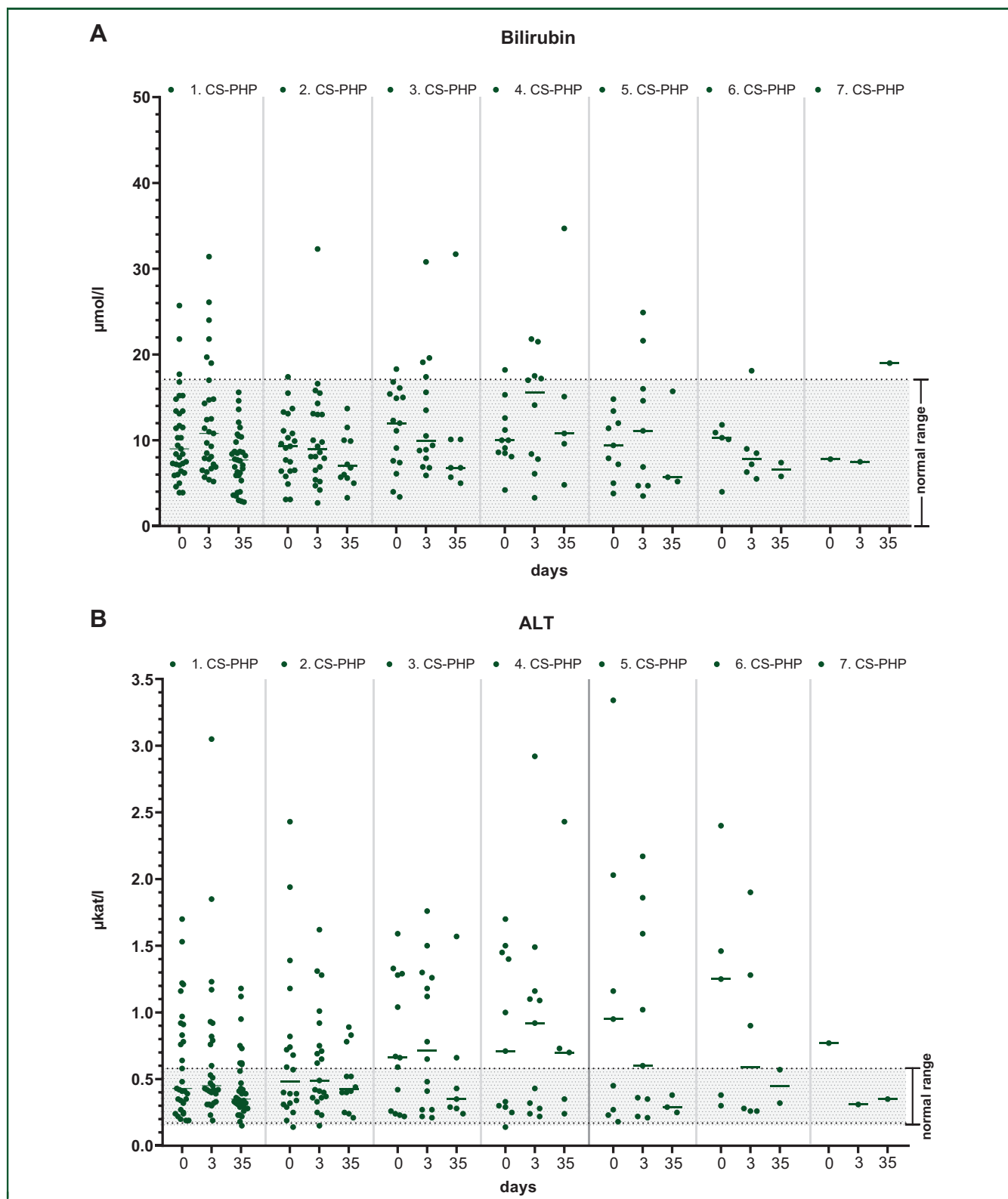


Figure 5. Liver related laboratory testings during CS-PHP. (A) Individual levels and medians of bilirubin levels after multiple courses of CS-PHP treatment. CS-PHP was carried out on day 0. (B) Individual levels and medians of ALT after multiple courses of CS-PHP treatment. CS-PHP was carried out on day 0. ALT, alanine aminotransferase; CS-PHP, chemosaturation with percutaneous hepatic perfusion.

switched to tebentafus. Another UM patient with a human leukocyte antigen (HLA)-A*02:01-positive mutation was treated with tebentafus after significant bone metastasis progression. A patient with ciliary body carcinoma, initially

responding intrahepatically, had progressive extrahepatic tumors and received gemcitabine and treosulfan, and then nivolumab and ipilimumab, without stabilization. All three died from tumor progression.

Four patients discontinued therapy due to travel difficulties and died from unknown causes. Four ICC patients switched from CS-PHP to standard chemotherapy or selective internal radiation therapy, showing disease progression and ultimately death. One young patient with clear-cell HCC received CS-PHP as a salvage treatment despite ascites and died during follow-up.

DISCUSSION

Our retrospective analysis evaluated the efficacy and long-term safety of CS-PHP for treating liver malignancies, irrespective of extrahepatic tumor manifestation, highlighting its potential in managing primary and secondary liver cancers. CS-PHP was carried out 97 times (median 2, range 1-7 per patient) in 33 patients. In the total population of 33 patients, the median hPFS was 52 weeks (SE 13.9, 95% CI 24.7-79.2 weeks) for all patients. Thirty patients (91%) showed hepatic disease control during CS-PHP. Response to CS-PHP, including hPR, hCR or hSD, and OS were similar in patients with or without extrahepatic tumor manifestation.

The majority of patients in our cohort had liver metastases from UM. Given that liver metastasis affects ~80% of UM patients and significantly reduces survival to an average of 6 months,²³ our findings underscore the critical need for effective treatment. Treatment options for hepatic UM are sparse as most patients will present with multilocular hepatic tumor infiltration making surgical resection impossible.²⁴ In January 2022, tebentafusp received FDA approval for the treatment of HLA-A*02:01-positive unresectable or metastatic UM.¹⁸ Eligibility criteria for the use of tebentafusp, requiring HLA-A*02:01, restrict its application to ~12% of African or African American and 27% of European descent patients, highlighting a significant treatment gap.²⁵ In recently published data of the open-label, phase III trial in which HLA-A*02:01-positive patients with previously untreated metastatic UM were randomly assigned in a 2 : 1 ratio to receive tebentafusp or a therapy with pembrolizumab, ipilimumab or dacarbazine, patients receiving tebentafusp showed a mean OS of 21.6 months as compared to 16.9 months in the control group receiving treatment with pembrolizumab, ipilimumab or dacarbazine.²⁶ With all the caution associated with this comparison, our UM patient population ($n = 19$) achieved a mean OS from first diagnosis of hepatic metastases of 20.59 months (range 2-63 months), indicating comparable survival results as HLA-A*02:01-positive patients receiving tebentafusp.

Our real-world data corroborate the efficacy of CS-PHP against UM hepatic metastases, aligning with outcomes observed in phase III and phase II trials, thereby reinforcing its clinical relevance.^{2,7,11,13-16,19,27-31} Moreover, CS-PHP as long-term treatment could have the potential to lead to comparable results as tebentafusp in HLA-A*02:01-positive patients and offers an equivalent treatment option. The great importance of controlling intrahepatic tumor manifestation for OS in our study, as well as the different approaches of the two treatment methods, should prompt us

to consider whether a combination treatment of CS-PHP and tebentafusp might be useful.

Besides patients with UM, our population included eight patients with ICC receiving a total of 17 CS-PHP treatments. The median OS from first CS-PHP treatment was 38 weeks (SE 2.9, 95% CI 32.0-43.7 weeks). Indeed, one of our patients suffering from ICC received CS-PHP as first-line treatment due to rapidly progressive tumor growth. In total, four CS-PHP treatments were carried out and hSD was maintained. Tumor progression halted over the observation period of 12 months. Such early and durable responses of ICC to treatment are of special interest as they rarely occur during systemic treatment with chemotherapy.^{32,33} Our findings coincide with a recently published study in 15 patients with ICC treated with repeated CS-PHP treatments.¹⁵ In this study by Marquardt et al., ORR was 20%, and disease control was achieved in 53% after the first CS-PHP. Median OS was 26.9 months from initial diagnosis and 7.6 months from first CS-PHP, and patients with liver-only disease had a significantly longer median OS compared to patients with locoregional lymph node metastases (12.9 versus 4.8 months, respectively; $P < 0.01$). The potential role of CS-PHP for the treatment of ICCs needs to be further investigated in prospective trials (Figure 1).

Our approach of using CS-PHP in the form of regularly repeated treatment cycles with undefined frequency (Figure 3), similar to systemic chemotherapy, resulted in long-term disease control in the majority of patients (Figure 2) and was well tolerated.

Even after multiple repetitions, there was no increase in CS-PHP-related AEs or liver toxicity.

Melphalan, an alkylating agent, induces DNA damage by attaching alkyl groups, resulting in DNA mismatches and strand breaks, leading to cell death. Its ability to be filtered from the blood makes it suitable for CS-PHP.¹⁰

Liver-related biochemical parameters were only transiently affected by CS-PHP and spontaneously returned to initial values at day 35 after each CS-PHP treatment in most patients (Figure 5). There was no accumulation of toxicity even after repeated applications.

Another argument for long-term repetition of CS-PHP deduced from our findings is that the initial decrease in tumor mass seen in all patients showing an initial response to CS-PHP remained stable during the observation period, and continued to further decrease after treatment repetitions in some patients (Figure 3). Interestingly, the tumor in one UM patient decreased below the visualization limit after six CS-PHP treatments (Figure 4A). We feel that the optimal frequency of CS-PHP and the timing of tumor staging must be defined urgently, as treatment success may only be achieved after several treatments (similar to systemic chemotherapy). In this context, it also needs to be investigated whether treatment with CS-PHP with melphalan in combination with, for example, immune checkpoint inhibitors as standard treatment might lead to even better response to CS-PHP.

In our patient population, patients with or without extrahepatic tumor manifestation at the start of CS-PHP, as well as those developing extrahepatic metastases during CS-PHP, showed similar OS as compared to those patients with liver-limited tumor. Ours is a very exploratory and underpowered analysis, but we believe that this observation highlights the importance of hepatic disease control for survival in our population of patients with hepatic tumor metastases. However, it must be mentioned that patients with extrahepatic metastases were selected for CS-PHP only if, according to the tumor board's assessment, no life-threatening disease dynamics were to be expected. Prospective trials on the value of CS-PHP in patients with limited extrahepatic tumor need to be conducted to clarify the potential of CS-PHP as part of a multimodal treatment approach of different tumor manifestations.

All types of CS-PHP-related AEs in our study are in accordance with those reported in previous studies.^{8,9,29,34} Hematological toxicity was common but transient and manageable; however, when grade III or IV occurred, treatment options were reconsidered. Importantly, AEs did not seem to increase in severity after multiple CS-PHP cycles in the majority of patients. Medication-related AEs only occurred in patients with ICC, one of whom had suspected systemic melphalan diffusion. Potential differences in melphalan washout in hepatic UM and ICC may be associated with our observation, which should be investigated.

Despite achieving good intrahepatic tumor control, CS-PHP presents significant obstacles. Its invasiveness, requirement for a skilled team, and high costs are major factors. Additionally, logistical challenges like long journeys, financial burdens, and post-treatment well-being issues have led to treatment interruptions for some patients. These factors must be carefully considered when opting for this treatment.

Future studies should aim to streamline treatment modalities and manage side-effects to reduce barriers to CS-PHP use and improve patient adherence.

The limitations of our study are the retrospective design, the limited patient number, the monocentric setting and inclusion of heterogeneous tumor types, as well as the lack of a control or comparator. Due to our study design and the loss to follow-up in four patients, AEs may have been underreported. Furthermore, there may be limited transferability of our data to other patient groups due to the monocentric conduct of our analysis and the hyperselected population. As our study was investigator-assessed, non-blinded and unconfirmed response assessments were used, this may lead to overestimation of the response rates.

We are convinced that our approach to use CS-PHP treatments needs to be validated in a prospective multicenter phase II clinical trial in comparison with standard of care.

CONCLUSION

Our results support the use of CS-PHP as a repeated long-term treatment in patients with primary or secondary liver tumors with or without extrahepatic tumor manifestations.

Repetition of CS-PHP for up to seven times led to stabilization of tumor growth in the majority of patients without accumulation of hepatic toxicity. Further clinical studies are warranted to develop CS-PHP as an effective treatment option for primary and secondary liver tumors.

FUNDING

This work was supported by institutional funding (no grant number).

DISCLOSURE

RV declares financial travel support from AbbVie, Eisai, Ipsen, Bayer, Delcath, as well as receipt of honoraria for advisory boards from Ipsen and Bayer. FL declares honoraria from honoraria for lectures and/or as an advisor from Amgen, Astellas, Astra Zeneca, Bayer, Biontech, BMS, Daiichi Sankyo, Eli Lilly, Elsevier, Falk Foundation, Incyte, Merck, MSD, Novartis, Roche, Servier, Springer-Nature, StreamedUp! His institution has received research support from Astra Zeneca, BMS and Gilead. TB declares receipt of grants/research supports from Abbvie, BMS, Gilead, MSD/Merck, Humedics, Intercept, Merz, Norgine, Novartis, Orphalan, Sequana Medical; receipt of honoraria or consultation fees/advisory board from Abbvie, Alexion, Albireo, Bayer, Gilead, GSK, Eisai, Enyo Pharma, HepaRegeniX GmbH, Humedics, Intercept, Ipsen, Janssen, MSD/Merck, Novartis, Orphalan, Roche, Sequana Medical, SIRTEX, SOBI and Shionogi; participation in a company sponsored speaker's bureau from Abbvie, Advance Pharma, Alexion, Albireo, Bayer, Gilead, Eisai, Falk Foundation, Intercept, Ipsen, Janssen, MedUpdate GmbH, MSD/Merck, Novartis, Orphalan, Sequana Medical, SIRTEX and SOBI. FvB declares honoraria from honoraria for lectures and/or as an advisor from ADVANZ Pharma, Astra Zeneca, Bayer, BMS, Falk Foundation, Gilead Sciences, MSD, Novartis, Roche, StreamedUp! All other authors have declared no conflicts of interest.

REFERENCES

- Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. *Int J Clin Exp Pathol*. 2013;6(7):1230-1244.
- Vogel A, Gupta S, Zeile M, et al. Chemosaturation percutaneous hepatic perfusion: a systematic review. *Adv Ther*. 2017;33(12):2122-2138.
- Aghemo A. Update on HCC management and review of the new EASL guidelines. *Gastroenterol Hepatol*. 2018;14(6):384-386.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236.
- Zager JS, Orloff MM, Ferrucci PF, et al. FOCUS phase 3 trial results: percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases (PHP-OCM-301/301A). *J Clin Oncol*. 2022;40(suppl 16):9510-9510.
- Burgmans MC, De Leede EM, Martini CH, Kapiteijn E, Vahrmeijer AL, Van Erkel AR. Percutaneous isolated hepatic perfusion for the treatment of unresectable liver malignancies. *Cardiovasc Intervent Radiol*. 2016;39(6):801-814.
- Vogl T, Zangos S, Scholtz J, et al. Chemosaturation with percutaneous hepatic perfusions of melphalan for hepatic metastases: experience from two European centers. *RöFo*. 2014;186(10):937-944.
- Forster MR, Rashid OM, Perez MC, Choi J, Chaudhry T, Zager JS. Chemosaturation with percutaneous hepatic perfusion for unresectable

- metastatic melanoma or sarcoma to the liver: a single institution experience. *J Surg Oncol*. 2014;109(5):434-439.
9. Miao N, Pingpank JF, Alexander HR, Steinberg SM, Beresneva T, Quezado ZMN. Percutaneous hepatic perfusion in patients with metastatic liver cancer: anesthetic, hemodynamic, and metabolic considerations. *Ann Surg Oncol*. 2008;15(3):815-823.
 10. Pingpank JF, Libutti SK, Chang R, et al. Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. *J Clin Oncol*. 2005;23(15):3465-3474.
 11. Savier E. Percutaneous isolated hepatic perfusion for chemotherapy: a phase 1 study. *Arch Surg*. 2003;138(3):325.
 12. Ferrucci PF, Cocorocchio E, Bonomo G, Varano GM, Della Vigna P, Orsi F. A new option for the treatment of intrahepatic cholangiocarcinoma: percutaneous hepatic perfusion with CHEMOSAT Delivery System. *Cells*. 2021;10(1):70.
 13. Kirstein MM, Marquardt S, Jedicke N, et al. Safety and efficacy of chemosaturation in patients with primary and secondary liver tumors. *J Cancer Res Clin Oncol*. 2017;143(10):2113-2121.
 14. Schneider AE, Sandor N, Karpati E, Jozsi M. Complement factor H modulates the activation of human neutrophil granulocytes and the generation of neutrophil extracellular traps. *Mol Immunol*. 2016;72:37-48.
 15. Marquardt S, Kirstein MM, Bruning R, et al. Percutaneous hepatic perfusion (chemosaturation) with melphalan in patients with intrahepatic cholangiocarcinoma: European multicentre study on safety, short-term effects and survival. *Eur Radiol*. 2019;29:1882-1892.
 16. Veelken R, Maiwald B, Strocka S, et al. Repeated percutaneous hepatic perfusion with melphalan can maintain long-term response in patients with liver cancers. *Cardiovasc Intervent Radiol*. 2022;45(2):218-222.
 17. Delcath Systems, Inc. Hepatic Delivery System for Melphalan Hydrochloride for Injection. 2021. Available at <https://chemosat.com/assets/product-manuals/germany/prev/120054D-EN-Commercial-for-DE-NL-120055D.pdf>. Accessed February 8, 2021.
 18. Montazeri K, Pattanayak V, Sullivan RJ. Tebentafusp in the treatment of metastatic uveal melanoma: patient selection and special considerations. *Drug Des Devel Ther*. 2023;17:333-339.
 19. Glazer ES, Zager JS. Chemosaturation with percutaneous hepatic perfusion in unresectable hepatic metastases. *Cancer Control*. 2017;24(1):96-101.
 20. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30(01):52-60.
 21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
 22. Struck MF, Kliem P, Ebel S, et al. Percutaneous hepatic melphalan perfusion: single center experience of procedural characteristics, hemodynamic response, complications, and postoperative recovery. *PLoS One*. 2021;16(7):e0254817.
 23. Pereira PR, Odashiro AN, Lim LA, et al. Current and emerging treatment options for uveal melanoma. *Clin Ophthalmol*. 2013;7:1669-1682.
 24. Caralt M, Martí J, Cortés J, et al. Outcome of patients following hepatic resection for metastatic cutaneous and ocular melanoma. *J Hepato Biliary Pancreat Sci*. 2011;18(2):268-275.
 25. Olivier T, Haslam A, Tuia J, Prasad V. Eligibility for human leukocyte antigen-based therapeutics by race and ethnicity. *JAMA Netw Open*. 2023;6(10):e2338612.
 26. Hassel JC, Piperno-Neumann S, Rutkowski P, et al. Three-year overall survival with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2023;389:2256-2266.
 27. Boone BA, Perkins S, Bandi R, et al. Hepatic artery infusion of melphalan in patients with liver metastases from ocular melanoma. *J Surg Oncol*. 2018;117(5):940-946.
 28. Hughes MS, Zager J, Faries M, et al. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. *Ann Surg Oncol*. 2016;23(4):1309-1319.
 29. Artzner C, Mossakowski O, Heffernan G, et al. Chemosaturation with percutaneous hepatic perfusion of melphalan for liver-dominant metastatic uveal melanoma: a single center experience. *Cancer Imaging*. 2019;19(1):31.
 30. Vogl TJ, Koch SA, Lotz G, et al. Percutaneous isolated hepatic perfusion as a treatment for isolated hepatic metastases of uveal melanoma: patient outcome and safety in a multi-centre study. *Cardiovasc Intervent Radiol*. 2017;40(6):864-872.
 31. Schönfeld L, Hinrichs JB, Marquardt S, et al. Chemosaturation with percutaneous hepatic perfusion is effective in patients with ocular melanoma and cholangiocarcinoma. *J Cancer Res Clin Oncol*. 2020;146(11):3003-3012.
 32. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281.
 33. Oh DY, Ruth He A, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evid*. 2022;1(8):EVID02200015.
 34. Struck MF, Werdehausen R, Kirsten H, et al. Prognostic factors for postoperative bleeding complications and prolonged intensive care after percutaneous hepatic chemosaturation procedures with melphalan. *Cancers*. 2023;15(15):3776.