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ORIGINAL ARTICLE

Transarterial chemoembolisation with irinotecan (irinotecan-TACE) as salvage or post-inductive therapy for colorectal cancer liver metastases: effectiveness results from the CIREL study

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Background: A pan-European, prospective, observational study on the use of irinotecan-eluting transarterial chemoembolisation (irinotecan-TACE) was conducted to evaluate effectiveness outcomes in salvage and post-inductive/consolidation therapy settings of colorectal cancer liver metastases (CRLMs).

Materials and methods: One hundred and fifty-two patients were consecutively enrolled between February 2018 and August 2020. All patients received irinotecan-TACE for CRLMs. Response data were assessed by a central independent image review panel according to RECIST v1.1. Prognostic factors for overall survival (OS), hepatic progression-free survival (HPFS), and progression-free survival (PFS) were calculated using multivariable Cox regression. Health-related quality of life (HRQoL) at the first follow-up was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

Results: One hundred and fifty-two (median age 66 years, 61% male) patients were prospectively enrolled. Overall, the median OS was 14.5 months [95% confidence interval (CI) 11.6-17.0 months]. The median OS (95% CI) of irinotecan-TACE as salvage therapy was 9.9 months (7.4-12.8 months) and the median PFS was 3.8 months (2.9-4.7 months). The median OS for post-inductive/consolidation therapy when used with systemic therapy or thermal ablation was 19.1 months (16.2-24.2 months), the median PFS was 6.0 months (4.5-8.7 months), and the median HPFS was 8.7 months (6.9-10.6 months).Following a multivariable analysis, negative prognostic factors for OS were Eastern Cooperative Oncology Group performance status $\geq$2 [hazard ratio (HR) 4.3], >50 mm lesion size (HR 2.1), progressive extrahepatic disease (HR 2.0), $\geq$2 prior systemic therapy lines (HR 2.4), >50% liver involvement (HR 8.5), and treatment plan not completed (HR 2.0). For PFS, progressive disease outside the liver (HR 1.8) and liver involvement of 25%-50% (HR 2.0) or >50% (HR 3.4) were identified as negative prognostic factors. HRQoL was generally stable or improved overall.

Conclusions: The results from the largest, pan-European, real-life study on irinotecan-TACE for CRLMs show a comparably long median OS when used as salvage therapy and promising HPFS when used with systemic therapy or thermal ablation as post-inductive/consolidation therapy. With its potential to maintain HRQoL, irinotecan-TACE could be further integrated into systemic treatment pathways.

Key words: interventional radiology, TACE, chemoembolisation, CRLM

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INTRODUCTION

The liver is the most frequent site of metastatic foci from colorectal cancer (CRC), with up to 25% of CRC patients presenting with colorectal cancer liver metastases (CRLMs) at the time of diagnosis and 30%-50% developing CRLMs in the first 2 years.[1] CRLMs are still the most frequent cause of death in CRC patients.

Potentially curative treatment options like surgical resection or any thermal ablation [microwave ablation (MWA), radiofrequency ablation (RFA), cryoablation], alone or in combination with a multimodal approach including systemic therapy, may represent a local treatment option for a relevant number of patients. However, a relevant proportion of patients are diagnosed with unresectable and/or 'unablatable' CRLMs and cannot be locally treated with a curative intent.[2]

For those patients, early-line systemic treatment includes combinations of fluoropyrimidines and either irinotecan or/and oxaliplatin, plus anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor targeted agents, or for patients with mismatch repair-deficient/microsatellite instability-high tumours, immunotherapy, depending on many clinical and molecular factors. As those regimens are highly effective, reduction of size of metastases (tumour downsizing) is frequently observed. As a result, the de-escalation of the initial combination treatment intensity to a 'maintenance therapy' can be implemented to minimise the risk of disease progression while balancing the adverse effect burden which adversely affects the quality of life and cognitive functioning of patients.[3-5] For later lines of treatment, trifluridine/tipiracil plus anti-VEGF (bevacizumab) is now considered the best treatment option in the third-line setting.[6,7] Beyond that, salvage therapy with regorafenib or fruquintinib may be contemplated.[8-10]

Transarterial chemoembolisation using irinotecan-eluting beads (irinotecan-TACE) is a locoregional treatment option that delivers sustained and targeted high-dose irinotecan to the metastatic liver while minimising systemic toxicity.[11-14] There is only limited evidence of when and for whom should irinotecan-TACE be preferred over other locoregional treatments or may be added to other treatments.

Irinotecan-TACE has generally been used as a 'salvage' therapy in patients who have progression after prior systemic treatments. Prospective and retrospective data have shown prolonged survival and tumour response with irinotecan-TACE as a stand-alone treatment or in combination with systemic treatments.[15-17]

Besides salvage therapy, irinotecan-TACE has also been evaluated as a 'post-inductive/consolidation' therapy combined with earlier lines of systemic therapy to consolidate the treatment effect.[18,19] This approach could be especially promising in the treatment plan after several cycles of systemic treatments allowing for the interruption or permanent discontinuation of 'maintenance therapy' by controlling the disease via irinotecan-TACE. In the context of post-inductive/consolidation therapy, the combination treatment of TACE and thermal ablation, particularly MWA or RFA, could be used to successfully treat lesions >3 cm which are typically considered too large for thermal ablation alone.[20]

Irinotecan-TACE can thus be potentially used either as a salvage therapy to achieve tumour control or as a post-inductive/consolidation therapy in a combined approach to consolidate the effect of a systemic therapy or thermal ablation.

CIREL provides a pan-European perspective using prospective, real-life data from >150 patients. Being the largest prospective study on irinotecan-TACE for CRLMs to date, CIREL has generated robust results on overall survival (OS), progression-free survival (PFS), hepatic progression-free survival (HPFS), and health-related quality of life (HRQoL) which may help physicians to guide their clinical decision making in this patient population.

MATERIALS AND METHODS

Study design

CIREL was a multicentre, prospective, observational study conducted in 11 European countries including 20 centres and enrolled 152 patients. In the initial stages of the study, a methodology manuscript outlined the study design and patient selection criteria.[21] An interim 50-patient analysis was also reported, with preliminary results on treatment intention, safety, and quality-of-life outcomes,[22] which was followed by the full-cohort publication on treatment intention, safety, and feasibility.[23]

The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable international and national regulations, and was approved by the ethics committees of all participating centres. All patients had at least one treatment session with irinotecan-TACE using LifePearl™ microspheres (LP-IRI) (MicroVention Europe, Saint-Germain-en-Laye, France). All other technical aspects of the treatments were determined by the treating physicians, who had the discretion to choose the most suitable approach for each patient.[23] Follow-up visits were suggested to be conducted 4-8 weeks and 12-16 weeks after the last treatment session, and then every 8 weeks until loss to follow-up, death, or until the end of data collection.

Data were collected via electronic case report forms using OpenClinica 3 (OpenClinica, LLC, Needham, MA). Data quality was ensured via automated data checks and verifications. Quarterly remote monitoring was conducted to resolve inconsistencies. No source data validation was carried out. Data modification was avoided as far as possible, if data points were modified by regrouping and for any processing to calculate endpoints, internal quality control was employed and where necessary validated by the multidisciplinary steering committee of the study.

Patients

Patients aged ≥18 years with histologically confirmed CRLMs were eligible for inclusion in the study after decision to be

treated with irinotecan-TACE by a multidisciplinary team (MDT). All patients provided written informed consent before enrolment. There were no predefined exclusion criteria.

Study endpoints

The primary endpoint of the study was to assess the number of indications that the device is being used for as assessed by stage and previous treatment(s). For that, the use of irinotecan-TACE was categorised into two treatment intentions: (i) 'salvage therapy' for patients who had progression after at least one line of systemic therapy and (ii) 'post-inductive/consolidation therapy' with irinotecan-TACE before/after systemic therapy or before/after other local ablative measures (mostly MWA).

Those groups deviate slightly from a previously published methodology of capturing a detailed treatment intention as this granular distinction could not be transformed into the daily routine situations of a real-world data setting.[21] Therefore, the steering committee made the decision to simplify the treatment intention groups. Two of the (initial) treatment intention groups, namely 'intensification of treatment with concomitant systemic therapy' and 'salvage treatment in progressive patients pre-treated with systemic therapy, with or without concomitant systemic therapy', were merged into one group titled 'salvage therapy'. Additionally, the three remaining treatment intention groups were merged by first merging 'LP-IRI as a first-line treatment' and 'LP-IRI as a consolidation or closing treatment with or without systemic therapy' by individual patient history assessment with two experts from the steering committee and then, 'combination treatment with ablation with curative intent' was also merged into the new group, termed 'post-inductive/consolidation therapy'. Statistically significant differences between merged groups were assessed. Statistically significant differences were detected only for group-defining factors, except for the number of treatment sessions per patient, which was higher in the 'first line or consolidation treatment after response to first-line systemic therapy' group compared with 'combination treatment with ablation with curative intent' and more patients with grade $\geq$1 increase of CA 19-9 in the 'intensification of treatment with concomitant systemic therapy' group than in the 'salvage treatment in progressive patients pre-treated with systemic therapy, with or without concomitant systemic therapy' group (data not shown). The groups were deemed similar enough to merge.

For secondary endpoints, RECIST version 1.1 (v1.1) was used to analyse objective response rate (ORR) as the proportion of patients with complete response (CR) or partial response (PR); disease control rate (DCR) as the proportion of patients with CR, PR, or stable disease; early tumour shrinkage of $\geq$20% and $\geq$30% of this initial (baseline) tumour size at follow-up 1; and depth of response.

Additional secondary endpoints included OS and HPFS, PFS according to RECIST v1.1, as well as a multivariable analysis of their prognostic factors. OS was analysed as the time between the first treatment administration of irinotecan-TACE and death, HPFS as the time between the first treatment administration of irinotecan-TACE and progression in the liver or death, and PFS as the time between the first treatment and progression or death.

For HRQoL, the global health score, the function score and its sub-scores, as well as the symptom score and its sub-scores were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) processed according to the EORTC scoring manual.[24]

Baseline data were collected on demographics, disease characteristics (of the primary tumour and treatment history), manifestations of liver metastases and extrahepatic metastases, and specifically for irinotecan-TACE: treatment intention and a detailed treatment plan. The treatment plan was considered complete based on whether all planned irinotecan-TACE treatment sessions could be carried out. Survival status, progression in the liver or outside the liver, and concomitant or subsequent treatments were collected continuously. At baseline, follow-up 1 (0.5-2.5 months), and follow-up 2 (2.7-6.9 months), computed tomography (CT) or magnetic resonance imaging (MRI) images for an independent image review according to RECIST v1.1 were collected. HRQoL was assessed at baseline and at 0.5-3.6 months using the EORTC QLQ-C30 questionnaire.[24,25] Remote monitoring was used to review and query the data, as well as to ensure consecutive patient enrolment.

Statistical analysis

Descriptive statistics were used to summarise patient characteristics, treatment patterns, and the primary endpoint. The Kaplan—Meier method was used to estimate median OS, HPFS, and PFS and the 95% confidence intervals (CIs). Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for OS, HPFS, and PFS. Variable selection was done by univariate analyses with a significance level of 0.1 and subsequent stepwise backwards selection to find the model with the best fit according to the likelihood ratio test. For the global health and the function score, high scores indicate high health and for the symptom score, low scores indicate few symptoms. Waterfall plots were used to show the difference between baseline and follow-up 1 per patient. The *P* values presented on those waterfall plots were calculated using the paired Wilcoxon rank test between baseline and follow-up 1 values. For comparisons of deterioration between patients with 0-1 lines of prior systemic treatment and patients with $\geq$2 lines, and to assess statistically significant differences between groups to be merged, the chi-square test was used. The cut-off for deterioration was defined as a change of at least 10 points. Data were censored the last time it was known, and no imputation was done for missing data. All statistical analyses were carried out using R Studio version 2023.03.0 (Posit, 2009, Boston,

MA) under R 4.3.1 (R Core Team, 1993; R Foundation for Statistical Computing, 2003, Vienna, Austria) and a two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Demographics and baseline characteristics

The investigators were instructed to consecutively enrol all consenting patients with proven CRLMs decided to be treated with irinotecan-TACE by an MDT. As a result, 152 patients from 20 centres in 11 countries were included in February 2018 and August 2020, and followed up until April 2022. Differences in enrolment rates were observed between countries and sites (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.104292). The median follow-up inclusion according to the reverse Kaplan—Meier estimate was 22.8 months (95% CI 19.0-27.8 months).

Baseline characteristics are shown in Table 1. A comprehensive listing of all baseline and treatment characteristics has been reported previously.[23] 61.2% of patients were male and the median age was 66 years (range 37-90 years). The Eastern Cooperative Oncology Group (ECOG) performance status was score 0 for 58.6%, 1 for 34.2%, 2 for 6.6%, and 3 for 0.7% of patients. Left-sided colon tumours were seen in 47.4%, followed by rectal tumours (29.6%) and right-sided colon tumours (23.0%). Extrahepatic metastases were present in 56.6% of patients.

For the primary endpoint of the study, the assessment of the number of indications that irinotecan-TACE was being used for resulted in 57.2% as salvage therapy for patients who had progressive disease after at least one line of systemic therapy and 42.8% of patients received irinotecan-TACE as a post-inductive/consolidation therapy with irinotecan-TACE before/after systemic therapy or before/after thermal ablation (Table 1). The treatment plan could be completed for 72% of salvage therapy patients and for 89% of post-inductive/consolidation therapy patients.

Table 1. Patient demographics and baseline characteristics

Measurement	Reference	
Age (years)	Median (range)	66 (37-90)
Sex, *n* (%)	Male	93 (61.2)
	Female	59 (38.8)
ECOG performance status, *n* (%)	0	89 (58.6)
	1	52 (34.2)
	2	10 (6.6)
	3	1 (0.7)
Primary tumour location, *n* (%)	Rectum	45 (29.6)
	Right colon	35 (23.0)
	Left colon	72 (47.4)
Tumour biology, *n* (%)	*RAS* mutation[a]	48 (31.6)
	BRAF V600E mutation[a]	9 (5.9)
	Double wild type	33 (21.7)
	Not available	64 (42.1)
Liver involvement, *n* (%)	<25%	82 (53.9)
	25%-50%	59 (38.8)
	>50%	11 (7.2)
Total number of lesions, *n* (%)	1	24 (15.8)
	2-3	46 (30.3)
	4-10	53 (34.9)
	>10	29 (19.1)
Prior systemic treatment, *n* (%)	5-Fluoruracil	110 (72.4)
	Oxaliplatin	93 (61.2)
	Irinotecan	87 (57.2)
	Anti-VEGF	53 (34.9)
	Anti-EGFR	25 (16.4)
	Trifluridine/tipiracil (TAS102)	12 (7.9)
Lines of systemic treatment, *n* (%)	0 lines	24 (15.8)
	1 line	66 (43.4)
	2 lines	46 (30.3)
	≥3 lines	16 (10.5)
Presence of extrahepatic metastases, *n* (%)	Yes	86 (56.6)
	No	66 (43.4)
CEA, *n* (%)	≤200 ng/ml	93 (61.2)
	>200 ng/ml	40 (26.3)
	Not available	19 (12.5)
Treatment intention, *n* (%)	Post-inductive/ consolidation therapy	65 (42.8)
	Salvage therapy	87 (57.2)

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.
[a]Two patients are double-mutant: the number adds up to 152 + 2.

Whole cohort early and long-term effectiveness

Tumour response according to RECIST v1.1 is depicted in the waterfall plots in Figure 1A showing the depth of response (see also Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.104292). For the 91 patients in whom independent image review was available at follow-up 1 or follow-up 2, the ORR was 9.9% (95% CI 6.2% to 11.5%) with 3 patients showing a CR and 6 patients a PR. Five patients (55.5%) with CR or PR received irinotecan-TACE as salvage therapy. MRI and angiogram images demonstrate how during the treatment of a subcapsular liver lesion (Figure 2A) with irinotecan-TACE, the contrast uptake that is present before the irinotecan-loaded bead injection (Figure 2B) stops after the injection (Figure 2C). The MRI image at the first follow-up visit shows a CR of the lesion (Figure 2D).

The duration of response and whether they had received systemic treatment before, concomitantly, or subsequently are shown in Figure 1B. Seventy-eight percent had received systemic treatment before irinotecan-TACE of which 18.4% either continued the systemic therapy throughout the irinotecan-TACE treatment plan or received it thereafter.

The median OS for the whole cohort was 14.5 months (95% CI 11.6-17.0 months), with 6- and 12-month OS rates of 82% and 55%, respectively (Figure 2E). While 36% of patients were censored, 44% of those were due to the end of the follow-up inclusion and the patient had been still alive. Multivariable Cox regression analysis revealed several significant prognostic factors for OS, including ECOG performance status ≥2 (HR 4.27, 95% CI 1.83-9.95), incomplete treatment plan (HR 2.04, 95% CI 1.12-3.70), lesion size >50 mm (HR 2.09, 95% CI 1.15-3.80), liver involvement of >50% (HR 8.47, 95% CI 3.53-20.35), ≥2 lines of prior systemic treatment (HR 2.35, 95% CI 1.24-4.44), and progressive disease outside the liver before treatment (HR 1.97, 95% CI

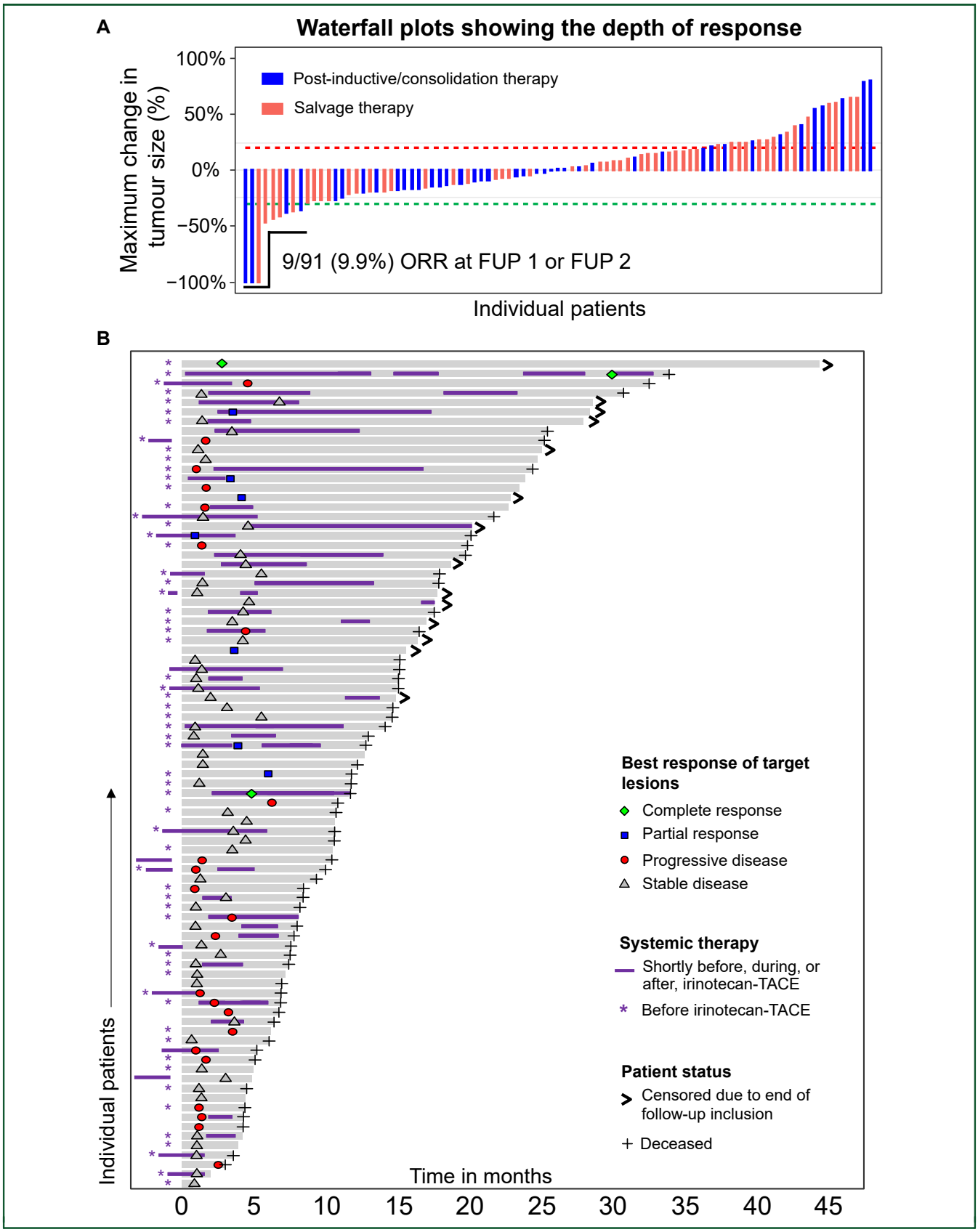

Figure 1. Depth and duration of response, according to RECIST 1.1. (A) Waterfall plot illustrating the depth of response. Each vertical bar represents an individual patient's best response of follow-up 1 or follow-up 2, with positive values indicating tumour growth and negative values indicating tumour shrinkage. Results from patients treated as 'post-inductive/consolidation' therapy are indicated in blue, results from patients treated as 'salvage therapy' are indicated in red. (B) Swimmer plot showing the duration of response and subsequent systemic treatments. Each horizontal line represents an individual patient, with the length of the line

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1.01-3.86) but not the presence of extrahepatic metastases in general (Table 2, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104292).

The median PFS was 4.6 months (95% CI 3.9-5.5 months) with 6- and 12-month PFS rates of 40% and 16%, respectively (Figure 2F). Progressive disease outside the liver (HR 1.81, 95% CI 1.06-3.09) and liver involvement of 25%-50% (HR 2.01, 95% CI 1.35-3.00) and >50% (HR 3.43, 95% CI 1.60-7.35) were found as significant prognostic factors in a multivariable Cox regression analysis (Table 2). The presence of extrahepatic metastases in general did not influence PFS (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104292).

The median HPFS was 6.2 months (95% CI 5.0-7.1 months) with 6- and 12-month HPFS rates of 52% and 24%, respectively (Figure 2G). Liver involvement of 25%-50% (HR 2.42, 95% CI 1.62-3.60) and >50% (HR 5.36, 95% CI 2.69-10.66), incomplete treatment plan (HR 1.89, 95% CI 1.16-3.07), and progressive disease in the liver (HR 2.30, 95% CI 1.16-4.54) were found as significant prognostic factors in a multivariable Cox regression analysis (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.104292). Neither the presence of extrahepatic metastases nor disease status of those was found to affect HPFS (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104292).

Subgroup effectiveness

For patients with irinotecan-TACE as salvage therapy, the median OS from first TACE procedure was 9.9 months (95% CI 7.4-12.8 months) with a 9-month OS rate of 53%. The median PFS was 3.8 months (95% CI 2.9-4.7 months), with a 9-month PFS rate of 15%, and the median HPFS was 4.4 months (95% CI 3.6-6.2 months), with a 9-month rate of 18% (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.104292).

For patients with irinotecan-TACE as post-inductive/consolidation therapy, the median OS from first TACE procedure was 19.1 months (95% CI 16.2-24.2 months) with a 9-month rate of 79%, the median PFS was 6.0 months (95% CI 4.5-8.7 months), with a 9-month rate of 32%, and the median HPFS was 8.7 months (95% CI 6.9-10.6 months), with a 9-month rate of 48% (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.104292).

Patient-reported health-related quality of life

We collected baseline and follow-up EORTC QLQ-C30 questionnaires from 91 patients and analysed the changes in global health, function, and symptom scores.

When using a cut-off of 10 points to determine clinically significant change in HRQoL, a substantial proportion of patients reported stable (52%) or even improved (14%) global health scores. Seventy-five percent and 4% had stable or improved functioning, and 81% and 3% had stable or improved symptom scores (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.104292).

A more detailed analysis revealed that certain symptoms, including pain, nausea and vomiting, fatigue, and appetite loss, showed significant deterioration (Figure 3A). However, other symptoms such as constipation, diarrhoea, dyspnoea, insomnia, and financial difficulties did not exhibit significant deterioration. This contributed to significant declines in role functioning, social functioning, emotional functioning, and physical functioning (Figure 3B). There was no significant deterioration observed in cognitive functioning.

When comparing patients with 0-1 prior lines of systemic treatment with those with ≥2 prior lines (Figure 3C), we found that a significantly higher proportion of patients with ≥2 prior lines experienced a ≥10-point deterioration in global health (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.104292, Figure 3C). However, no significant differences were observed between the two groups regarding functioning or symptom scores.

DISCUSSION

For the complex clinical management of patients with CRLMs not eligible for a curative treatment approach, many factors should be considered. While locoregional liver-directed treatments such as irinotecan-TACE constitute a further treatment option, there is a need to better define the place of locoregional approaches in liver-limited or liver-dominant disease, irrespective of the systemic treatment history. This is especially important as comparability between irinotecan-TACE studies is difficult due to varying methodology, patient selection, and small sample sizes. Our full-cohort publication of the safety and feasibility of CIREL has already confirmed that irinotecan-TACE as a locoregional treatment for CRLMs is generally well tolerated and can be applied repeatedly due to its minimally invasive nature.[23]

With over 150 patients, this prospective registry represents the to date largest database on irinotecan-TACE for CRLMs providing a pan-European perspective on the real-life evidence. Our data highlight the variability of patients treated with irinotecan-TACE not only between countries but also between sites within the same country. This may be attributed to some MDTs considering irinotecan-TACE as a valuable treatment option while others valuing alternative therapies, including new systemic agents, rechallenging with previously used agents, or other locoregional therapies, such as transarterial radioembolisation. The majority of patients received irinotecan-TACE as a salvage therapy following progression after at most many but at least one line of systemic therapy (57%). In this indication, a median OS of 9.9 months (7.4-12.8 months) and a median PFS of

corresponding to the duration of follow-up in the study. Patients who have died are marked with a '+', patient who were confirmed to be alive at the end of the follow-up inclusion are marked with a '>'. Complete response is indicated by a bright green lozenge, partial response by a dark blue square, stable disease by a grey triangle, and progressive disease by a red circle. Prior, concomitant, and subsequent systemic therapy is indicated by a purple star or a purple line.
FUP, follow-up; ORR, objective response rate.

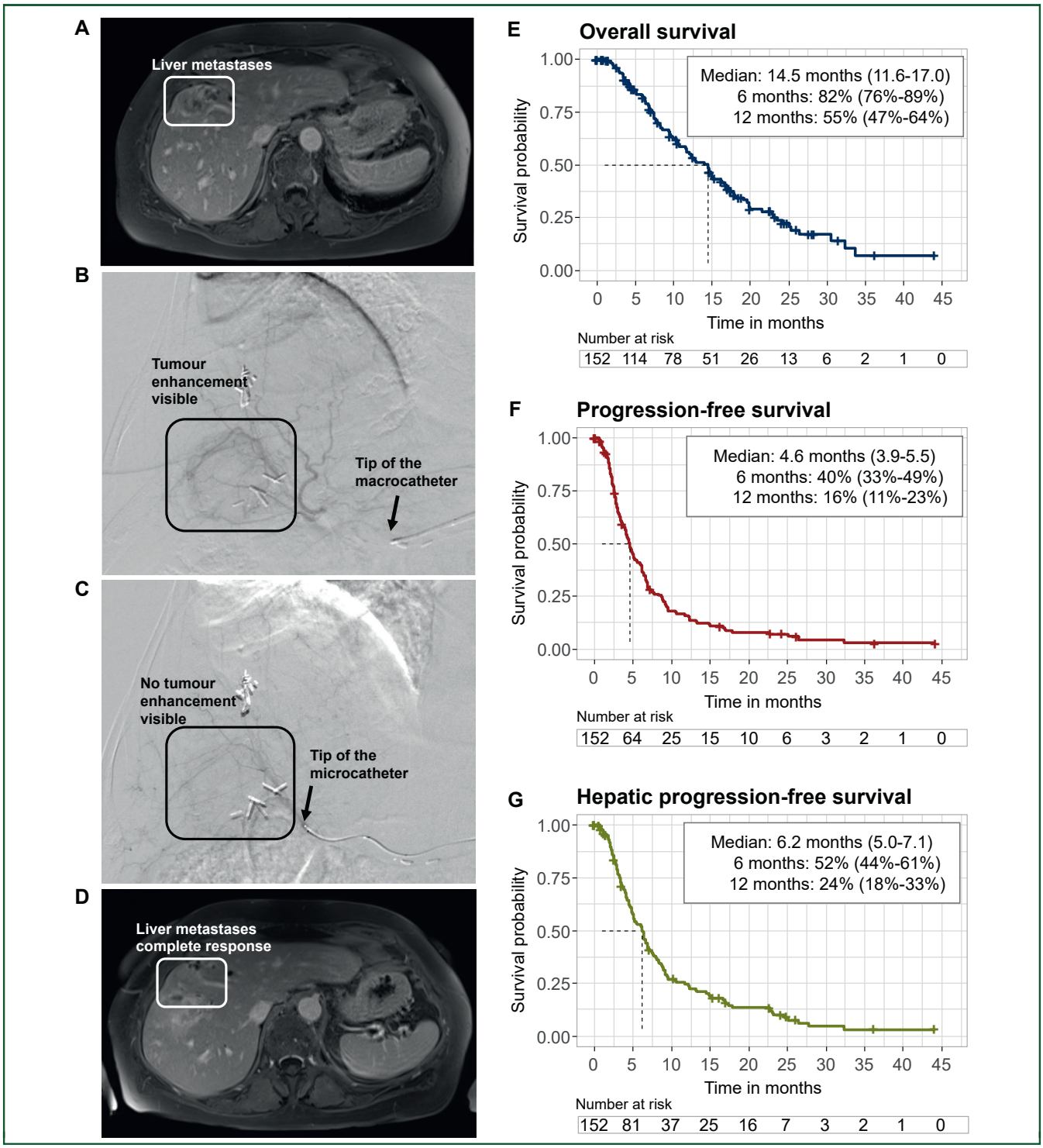

Figure 2. Effectiveness of irinotecan-TACE. Contrast-enhanced T1 fl2D MR image shows a subcapsular CRLM after surgical resection before irinotecan-TACE (A). Late arterial phase at angiogram after contrast injection showing the tumour blush (NB: surgical clips are well visible) (B). Late arterial phase after application of irinotecan-loaded microspheres 100 mg demonstrating the absence of tumour enhancement (C). MRI at first follow-up showing complete response. Survival plot and showing OS (E), PFS (F), and HPFS (G). Insets show the median OS, PFS, or HPFS, as well as the 6- and 12-month survival rate, according to RECIST v1.1. The 95% confidence interval of the Kaplan—Meier estimates is shown in parentheses.

CRLM, colorectal cancer liver metastasis; HPFS, hepatic progression-free survival MR, magnetic resonance; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolisation

3.8 months (2.9-4.7 months) were reported. The remaining 43% of patients included into this prospective registry had received irinotecan-TACE as post-inductive/consolidation therapy before/after systemic therapy or before/after/during thermal ablation. In these patients, a markedly longer median OS of 19.1 months (16.2-24.2 months) and a median PFS of 6.0 months (4.5-8.7 months) were documented. Since irinotecan-TACE is a locoregional treatment that acts directly in the liver, an HPFS of 8.7 (6.9-10.6) of the post-inductive/consolidation therapy should be highlighted.

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Table 2. Uni- and multivariable Cox regression for overall survival and progression-free survival

	Univariable			Multivariable	
	Median months (95% CI)	HR	*P* value	HR (95% CI)	*P* value
Overall survival					
Estimated burden of liver involvement					
<25%	17.0 (12.9-22.9)	—	—	—	—
25%-50%	10.6 (8.4-16.7)	1.84 (1.21-2.81)	0.005	1.39 (0.84-2.31)	0.203
>50%	4 (3.6-NA)	7.78 (3.42-17.71)	<0.001	**8.47 (3.53-20.35)**	**<0.001**
ECOG score					
0-1	14.5 (10.8-17.0)	—	—	—	—
≥2	14.0 (8.5-17.0)	0.38 (0.19-0.76)	0.006	**4.27 (1.83-9.95)**	**<0.001**
Number of previous lines of systemic treatment					
0 lines	19.1 (14.5-NA)	—	—	—	—
1 line	15.0 (12.0-24.2)	0.93 (0.51-1.71)	0.823	1.52 (0.78-2.96)	0.223
≥2 lines	8.5 (7.3-12.3)	1.86 (1.04-3.34)	0.037	**2.35 (1.24-4.44)**	**0.009**
Lesion size					
≤30 mm	18.1 (14.5-NA)	—	—	—	—
30-50 mm	16.2 (12.1-24.2)	1.71 (0.92-3.19)	0.921	1.58 (0.82-3.04)	0.174
>50 mm	9.5 (7.7-14.6)	2.53 (1.46-4.39)	<0.001	**2.09 (1.15-3.80)**	**0.016**
Treatment plan completed					
Yes	14.6 (12.3-17.5)	—	—	—	—
No	6.2 (3.4-NA)	2.16 (1.25-3.73)	0.006	**2.04 (1.12-.3.70)**	**0.020**
Tumour status outside the liver					
No disease	14.9 (12.3-18.1)	—	—	—	—
Partial/complete response	NA (4.2-NA)	0.24 (0.03-1.75)	0.160	0.28 (0.04-2.12)	0.215
Stable disease	10.6 (7.4-23.1)	1.02 (0.63-1.65)	0.931	0.71 (0.42-1.19)	0.195
Progressive disease	7.5 (4.1-NA)	2.18 (1.22-3.90)	0.009	**1.97 (1.01-3.86)**	**0.048**
Tumour status in the liver					
Partial/complete response	23.1 (8.5-NA)	—	—	—	—
Stable disease	22.9 (14.6-NA)	1.08 (0.39-2.98)	0.886	0.76 (0.25-2.30)	0.625
Progressive disease	12.3 (19.6-15.0)	1.82 (0.83-3.95)	0.132	1.89 (0.83-4.35)	0.132
Liver metastases diagnosis					
Metachronous	17.0 (10.5-22.9)	—	—	—	—
Synchronous	12.7 (10.7-15.1)	1.08 (0.69-1.68)	0.741	—	—
Concomitant systemic therapy					
Yes	10.6 (7.4-17.9)	—	—	—	—
No	14.6 (11.7-18.1)	0.69 (0.46-1.06)	0.090	—	—
Progression-free survival					
Estimated burden of liver involvement					
<25%	6.0 (4.6-8.9)	—	—	—	—
25%-50%	3.8 (2.7-5.1)	2.05 (1.42-2.96)	<0.001	**2.01 (1.35-3.00)**	**<0.001**
>50%	2.9 (2.5-NA)	3.25 (1.68-6.31)	<0.001	**3.43 (1.60-7.35)**	**0.002**
Tumour status outside the liver					
No disease	5.5 (4.6-6.7)	—	—	—	—
Partial/complete response	6.0 (2.6-NA)	0.66 (0.21-2.10)	0.484	0.65 (0.20-2.10)	0.472
Stable disease	3.0 (2.1-6.2)	1.25 (0.84-1.87)	0.279	1.16 (0.76-1.78)	0.485
Progressive disease	2.7 (2.5-6.7)	1.74 (1.04-2.92)	0.036	**1.81 (1.06-30.9)**	**0.030**
Primary tumour location					
Left colon	4.4 (3.0-6.7)	—	—	—	—
Rectum	5.5 (4.4-6.9)	0.97 (0.65-1.45)	0.886	1.10 (0.72-1.67)	0.652
Right colon	3.4 (2.7-6.2)	1.45 (0.93-2.24)	0.098	1.56 (0.96-2.52)	0.074
Lactate dehydrogenase increased					
Normal	5.1 (4.2-6.6)	—	—	—	—
Increased	4.2 (3.1-5.2)	1.42 (0.69-1.54)	0.050	1.23 (0.84-1.79)	0.290
Alanine aminotransferase increased					
Normal	5.1 (4.2-6.6)	—	—	—	—
Increased	3.5 (2.8-5.0)	1.51 (1.06-2.16)	0.024	—	—
Number of previous lines of systemic treatment					
0 lines	6.7 (4.8-9.4)	—	—	—	—
1 line	4.6 (3.8-6.2)	1.22 (0.74-2.00)	0.439	—	—
≥2 lines	3.8 (2.8-5.1)	1.53 (0.94-2.51)	0.088	—	—
ECOG score					
0-1	4.8 (4.0-6.2)	—	—	—	—
≥2	4.2 (3.4-6.4)	0.81 (0.42-1.54)	0.518	—	—
Lesion size					
≤30 mm	6.2 (4.4-9.5)	—	—	—	—
30-50 mm	4.6 (3.1-6.9)	1.50 (0.91-2.47)	0.111	—	—
>50 mm	4.1 (3.2-5.1)	1.87 (1.20-2.92)	0.006	—	—
Anatomical localisation of liver metastases					
Bilobar	4.2 (3.4-4.7)	—	—	—	—
Unilobar	5.5 (4.5-6.9)	0.74 (0.52-1.04)	0.087	—	—

Continued

Table 2. Continued

	Univariable			Multivariable	
	Median months (95% CI)	HR	*P* value	HR (95% CI)	*P* value
Treatment plan completed					
Yes	4.8 (4.2-6.2)	—	—	—	—
No	2.9 (2.0-6.2)	1.65 (1.05-2.59)	0.030	—	—

Values in bold represent factors that were retained in the final model and are statistically significant with a *P* value ≤0.05.
CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; NA, not available.

Our multivariable analysis across the whole cohort identified ECOG performance status ≥2 and having received ≥2 prior lines of systemic therapy as negative predictors for OS, which likely reflect a prolonged disease course and are commonly associated with patients considered for salvage therapy. Additionally, incomplete treatment plans emerged as a negative predictor for OS and HPFS, but not for PFS, likely due to untreated residual liver lesions. Similar to other studies, lesion size of ≥50 mm and >50% liver involvement were identified negative prognostic factors for OS.[16,26,27] Regarding the impact of extrahepatic disease on survival, the presence of progressive extrahepatic metastases was associated with poorer OS and PFS, unlike extrahepatic metastases in general. In our cohort, most patients with extrahepatic disease had a limited number of metastases to the lung, which have a better prognosis than metastases to other sites.[2] Due to the significant number of missing data points, we could not analyse the effect of *RAS* and *BRAF* mutations on survival; however, they have been reported as negative predictive factors by other real-world irinotecan-TACE studies.[16,28]

In previously reported studies, the overwhelming majority describe the efficacy of irinotecan-TACE for patients who had progression after at least one line of systemic therapy which corresponds to our salvage therapy group. The published efficacies span a wide range of median OS from 5 to 33 months,[26-35] with a recent meta-analysis calculating a weighted average of 16.8 months.[36] This is likely explained by small sample sizes and by differences in critical factors between the published cohorts. The most important factor seems to be whether those studies enrolled patients with extrahepatic disease. Cohorts that enrolled patients with liver-only disease have reported a median OS of 20-25 months.[29-33] Conversely, cohorts that enrolled patients with liver-dominant disease and did not exclude the presence of extrahepatic disease showed a median OS of 7-15 months,[26-28,34,35] with two exceptions showing medians around 19 months.[37,38]

Second-line systemic therapy generally results in a median OS and PFS of 11.5-13.4 and 4.5-6.4 months, respectively,[39,40] with real-world evidence showing a median OS of 14.04 months and a median PFS of 7.6 months.[41] For third line and beyond, the median OS has been reported between 7 and 9 months,[42] with real-world studies showing a median OS of 5.6-7.4 months for regorafenib[43-45] and 6.3-7.9 months for trifluridine.[44,45] In recent years, combining trifluridine with anti-VEGF antibodies, bevacizumab, resulted in median OS ranging between 9.3 and 14.9 months[46-50] in real-world settings. However, specific chemotherapy-associated toxicity, like neutropenia, can cause dose delays[48,50] and put frail patients at risk for serious infections and hospitalisations.[51]

Regarding the efficacy of post-inductive/consolidation therapy via combination of TACE with systemic treatment, studies are showing promising results. For example, FOLFOX + irinotecan-TACE as first line compared with FOLFOX + anti-VEGF resulted in a longer median PFS (15.3 versus 7.6 months).[18] On the contrary, 'maintenance systemic therapy' typically results in a PFS of 7.8-9.6 months calculated from the start of the induction therapy.[52-55]

In both cohorts of patients receiving either salvage or post-inductive/consolidation therapy, HRQoL considerations can contribute to a better understanding of patient-oriented treatment selection. Here, HRQoL was stable or improved in the majority of patients. Role and social functioning were affected the most; however, we found no significant differences in cognitive functioning. This effect could be attributed to four out of the nine symptom subscores (see Figure 3). The effect on few procedure-related symptoms is a testament to the potential of irinotecan-TACE for disease control.[23] This adds to the evidence of other studies concluding that irinotecan-TACE generally does not have a negative effect on HRQoL,[30,56,57] with one study showing that irinotecan-TACE may have favourable HRQoL outcomes compared with FOLFIRI.[29]

Ultimately, since irinotecan-TACE is a locoregional therapy that can be repeated for progressive or new lesions or followed up by other locoregional or systemic therapies, early response and disease control should not be neglected. The ORR and DCR results from our study were based on an independent centralised assessment according to RECIST v1.1. Generally, studies have reported ORR ranging between 50% and 78%.[29-31] Those differences could be due to the independent image review and/or assessment protocol variabilities. To have reliable early response data for future decisions about the treatment pathways, suitable ways of analysing and predicting tumour progression are required. The RECIST v1.1 criteria mainly focus on tumour size and could therefore potentially underrepresent the treatment effect by not accounting for tumour activity and tumour necrosis. Other criteria such as modified RECIST (mRECIST), Choi criteria, or evaluations based on positron emission tomography—CT which assess tumour necrosis/viability are also starting to find use in CRLMs.[58]

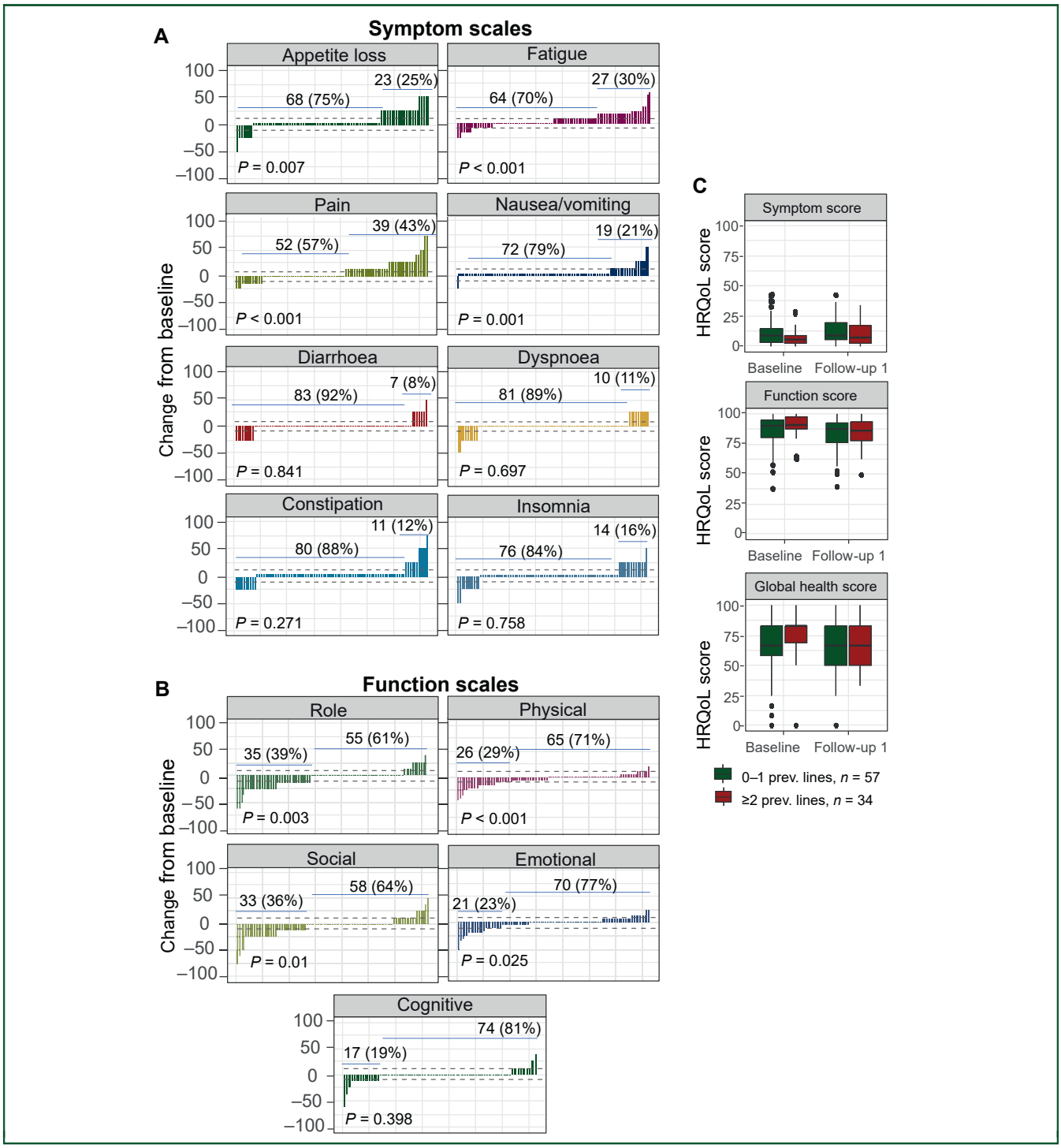

Figure 3. Health-related quality of life. Baseline: 0-1 months before the first treatment, follow-up 1: 0.5-3.6 months after the last treatment. Baseline questionnaires were only included if there was a corresponding follow-up 1 questionnaire. (A) Waterfall plots show the change of appetite loss, fatigue, pain, nausea/vomiting, diarrhoea, dyspnoea, constipation, and insomnia when comparing follow-up 1 with baseline. Each bar represents one patient. Higher values represent more symptoms and a worse symptom score. The *P* values presented on the waterfall plots are calculated using the paired Wilcoxon rank test between baseline and follow-up 1 values. (B) Waterfall plots showing the change of role functioning, physical functioning, social functioning, emotional functioning, and cognitive functioning when comparing follow-up 1 with baseline. Each bar represents one patient. Lower values represent lower functioning and a worse function score. The paired Wilcoxon rank test was used to calculate the *P* values. (C) Comparison between patients with 0-1 (orange) and ≥2 (blue) previous lines of systemic treatment for symptom, function, and global health scores at baseline and follow-up 1. Boxplot displays a box with the three lines representing Q1, median (Q2), and Q3, respectively. Upper whisker of Q3 + 1.5 × IQR, lower whisker of Q1 − 1.5 × IQR. Outlier values beyond the whiskers are displayed as circles.
HRQoL, health-related quality of life; IQR, interquartile range.

Limitations

This prospective observational study has limitations due to possible critical confounding factors that could not be controlled. The patient population's diversity across participating sites mirrors real-life clinical practice, resulting in varying patient selection and outcomes. While we

employed multivariable analysis to mitigate this heterogeneity to an extent, it is important to acknowledge that unaccounted confounding factors may influence the interpretation of the results. While the study has a relatively high number of censored patients regarding OS, 44% of all censored patients were still alive at the end of the study. The relatively high number of missing images for the central image review and HRQoL questionnaires can partially be explained by patients' deaths or study exit before data for follow-up 1 could be collected; therefore, the response estimates should be interpreted within the calculated 95% CI as this range likely contains the true population parameter with 95% certainty.

Conclusion

Our prospective pan-European study showed that in real-world practice, irinotecan-TACE is not only used as a 'salvage therapy' but also as a 'post-inductive/consolidation therapy together with systemic therapy or thermal ablation'. Moreover, our effectiveness data on irinotecan-TACE for CRLMs highlight the relatively long median OS when used as a salvage therapy and also show that irinotecan-TACE when used as a post-inductive/consolidation therapy achieves promising HPFS. Considering its minimally invasive and repeatable nature, as well as the potential for combination with other treatment strategies to either intensify the liver-directed treatment or target extrahepatic disease, randomised trials are needed to provide robust evidence on how irinotecan-TACE can be integrated into a treatment pathway that minimises patient burden while preserving HRQoL.

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TH received speaker honoraria from Sirtex Medical Europe. OP received honoraria for lectures from Merit Medical and he is a co-founder of PERSEA. JT reports receiving honoraria from Merck, Roche, Amgen, Lilly, Sanofi, Samsung, MSD, Servier, Celgene, Pierre Fabre; consulting or advisory role for Roche, Merck KGaA, Amgen, Lilly, MSD, Servier, Pierre Fabre, Sanofi, Samsung; and speakers' bureau for Servier, Amgen, Roche, Sanofi, Merck, Lilly, Pierre Fabre. GM received honoraria for speaker's bureau from Sirtex Medical and operated as a proctor for Sirtex. FMG received grants or contracts from Boston Scientific and iVascular; consulting fees from Boston Scientific, iVascular and Braun; honoraria for lectures from Canon and Siemens Healthineers; and payments for expert testimony from Boston Scientific. AG received consulting fees from Terumo; honoraria for lectures from Boston Scientific and the Boston Endovascular Excellence Academy; President of the Macedonian Association of radiologists—MAR; and President of the Society for interventional radiology of North Macedonia—SIRNM. BS received grants or contracts from BMS; consulting fees from AstraZeneca, Bayer, BMS, Boston Scientific, Eisai, Incyte, Ipsen, Roche, Sirtex Medical, Terumo; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Eisai, Incyte, Roche, Sirtex Medical; participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, Bayer, BMS, Boston Scientific, Eisai, Incyte, Roche, Sirtex Medical; and has a leadership or fiduciary role in the International Liver Cancer Association. DA received consulting fees from Boston Scientific, Terumo, MSD, BMS, AstraZeneca, Roche, Servier, Sanofi, Merck Serono, CRA International; honoraria for lectures or presentations from Boston Scientific, Terumo, BMS, MSD, AstraZeneca, Roche, Servier, Sanofi, Merck Serono, Amgen, Aptitude Health, Art tempi media, Boehringer Ingelheim, Clinical Care Options (CCO), Eisai, From Research to Practice, GSK, Imedex, IOMEDICO, PeerMD, PRMA Consulting, Sirtex, Steamitup Germany, Tactics MD LLC, Takeda, Viatris, WebMD Health Corp; travel support from Boston Scientific, Terumo, MSD, BMS, AstraZeneca, Roche, Servier, Sanofi, Merck Serono, Caiichi Sankyo; participated in Data Safety Monitoring Board or Advisory Board for Amgen, AstraZeneca, Boston Scientific, CRA International, Janssen Cilag, Merck Sharp & Dohme, Onkowissen, Seagen, Taiho, Takeda, Terumo; and he is also an Associate Editor for *ESMO Open*, *Ann Oncol*, and *Clin Colorect Cancer*. PLP received grants or contracts from Siemens Healthineers, Terumo, Medtronic, Angiodynamics, BMS, MSD, GSK; honoraria for lectures or presentations from Terumo, Sirtex, Angiodynamics, Medtronic, Pharmacept, Guerbet; and travel support from Bayer. All other authors have declared no conflicts of interest.

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