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Original Article

Hepatic arterial infusion pump chemotherapy combined with systemic chemotherapy for borderline resectable and unresectable colorectal liver metastases: phase II feasibility study

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Abstract

Background: Hepatic arterial infusion pump chemotherapy combined with systemic chemotherapy (HAIP-SYS) for liver-only colorectal liver metastases (CRLMs) has shown promising results but has not been adopted worldwide. This study evaluated the feasibility of HAIP-SYS in the Netherlands.

Methods: This was a single-arm phase II study of patients with CRLMs who received HAIP-SYS consisting of floxuridine with concomitant systemic FOLFOX or FOLFIRI. Main inclusion and exclusion criteria were borderline resectable or unresectable liver-only metastases, suitable arterial anatomy and no previous local treatment. Patients underwent laparotomy for pump implantation and primary tumour resection if *in situ*. Primary end point was feasibility, defined as ≥70% of patients completing two cycles of HAIP-SYS. Sample size calculations led to 31 patients. Secondary outcomes included safety and tumour response.

Results: Thirty-one patients with median 13 CRLMs (i.q.r. 6–23) were included. Twenty-eight patients (90%) received two HAIP-SYS cycles. Three patients did not get two cycles due to extrahepatic disease at pump placement, definitive pathology of a recto-sigmoidal squamous cell carcinoma, and progressive disease. Five patients experienced grade 3 surgical or pump device-related complications (16%) and 11 patients experienced grade ≥3 chemotherapy toxicity (38%). At first radiological evaluation, disease control rate was 83% (24/29 patients) and hepatic disease control rate 93% (27/29 patients). At 6 months, 19 patients (66%) had experienced grade ≥3 chemotherapy toxicity and the disease control rate was 79%.

Conclusion: HAIP-SYS for borderline resectable and unresectable CRLMs was feasible and safe in the Netherlands. This has led to a successive multicentre phase III randomized trial investigating oncological benefit (EUDRA-CT 2023–506194-35-00). **Current trial registration number**: clinicaltrials.gov (NCT04552093).

Introduction

In patients with colorectal liver metastases (CRLMs) confined to the liver, resection of all tumour sites may offer a chance of long-term survival and even cure. Unfortunately, most patients present with multiple and/or unresectable CRLMs[1,2]. Resection is a dominant contributor to long-term survival and efforts have been made to increase resection rates in these patients.

The CAIRO5 study investigated several induction systemic therapies (SYS) in patients with unresectable CRLMs and showed complete local treatment rates (including R0 or R1 resection and complete thermal ablation) varying from 37% to 58% depending on regimen, sidedness of the tumour and mutational status[3]. Despite high local treatment rates, recurrences were frequently observed. Within 2 years, 79% of patients experienced recurrent disease, predominantly in the liver.

Hepatic arterial infusion pump (HAIP) can deliver high-dose regional chemotherapy to the liver and improve response, conversion and survival rates according to studies performed at

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Memorial Sloan Kettering Cancer Center (MSKCC) in the USA[4–9]. Floxuridine (FUDR) is used in the pump because it has a high first-pass liver extraction rate of 95%, which results in limited systemic toxicity and enables a 400-fold higher dose compared to systemic administration[5,10,11]. Conversion-to-resection of unresectable CRLMs has been observed in up to 57% of chemo-naive patients and up to 38% of patients who had (one or more lines) prior systemic therapy[6,8,9,12]. HAIP-SYS resulted in median overall survival (OS) of 50.8–76.6 months and 19.5–35 months in chemo-naive patients and patients who received prior systemic therapy respectively. Corresponding 5-year OS were 51.9% and 27.9% respectively[5–9]. Conversion after HAIP-SYS has been associated with better survival[8].

Despite these impressive results, adoption of HAIP-SYS outside MSKCC has been limited, although several North American centres have started HAIP programmes recently[9,12–15]. Pumps as used in the USA harbour the propellant freon, which is not allowed in the EU due to its environmental hazard. Moreover, FUDR is not registered in the EU. This implies that this drug cannot be used outside studies. The treatment is intense for the patient and the team. The pump has to be filled every 2–3 weeks. Side effects may be caused by the HAIP component or the systemic component. When and how to proceed to conversion surgery is more challenging as the liver hilum is less accessible. From earlier experience in adjuvant HAIP the authors learned that a dedicated, experienced, multidisciplinary team is a prerequisite for the success of this complex treatment regimen, as experience in induction HAIP therapy for CRLMs was non-existing in the EU[16].

This phase II study was set up to assess feasibility, safety and efficacy of HAIP-SYS in patients with borderline resectable or unresectable CRLMs.

Methods

This was a single arm phase II study performed in the Netherlands Cancer Institute (NCI) and the Erasmus MC Cancer Institute, two tertiary referral centres for patients with stage IV colorectal cancer in the Netherlands. Both multidisciplinary teams (MDT) were proctored by the MSKCC team. Adult patients with WHO 0 or 1 status and an indication for systemic therapy for borderline resectable or unresectable CRLMs and without extrahepatic metastases were eligible. According to Dutch guidelines, patients with upfront unresectable CRLMs have an indication for systemic therapy, whereas this is not included in the default treatment of patients with resectable CRLMs. Neoadjuvant chemotherapy is considered in patients with unfavourable tumour characteristics including number, size and location and is determined by the MDT. There is no consensus among liver surgeons and MDTs on which patient has unresectable, borderline resectable or resectable metastases, as indicated by a substudy of the CAIRO5 study and the RAXO study, among others[3,17]. Criteria used in CAIRO5 included CRLMs that could not be sufficiently treated in a single procedure by resection only. Patients were classified as potentially resectable or likely permanent unresectable (that is, a combination of involved inflow and outflow of the left and right half of the liver). These criteria were used in the current study and patients were reported as having borderline resectable and unresectable metastases.

To allow for pump implantation, the gastroduodenal artery should be patent and in connection with at least one of the liver arteries. Other exclusion criteria were mismatch repair deficiency of the tumour, dihydropyrimidine dehydrogenase (DPD) deficiency, inadequate liver or renal function and previous local treatment of CRLMs. Previous systemic therapy was permitted in case there was no disease progression under irinotecan and/or oxaliplatin-based treatments. Full inclusion and exclusion criteria are available in *Table S1*.

Patients gave written informed consent. This study was registered at clinicaltrials.gov (NCT04552093) and approved by the medical ethics committee of the NCI and competent authorities (CCMO NL70112.031.19; EudraCT 2019-003260-44).

Study procedures are visualized in *Fig. S1*.

Surgery

Pump implantation, perioperative procedures, and HAIP (FUDR) dosages in the Netherlands have been described previously. The primary tumour was resected if *in situ*, with or without primary anastomosis at the discretion of the surgeon. First-stage hepatectomy was allowed if limited (that is, a wedge resection and ablation in the future liver remnant). Resection or biopsy of one of the CRLMs was encouraged to confirm metastasis.

HAIP-SYS administration

The start of HAIP-SYS was scheduled within 6 weeks following surgery. Start and stop dates of HAIP and systemic chemotherapy were determined separately. HAIP was scheduled every 4 weeks (2 weeks of continuous administration of FUDR followed by 2 weeks of heparin/saline solution). Concomitant administration of intravenous 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) was scheduled on the day of pump reservoir filling (every 2 weeks). The initial start dose of oxaliplatin was 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and 5-fluorouracil 2400 mg/m^2 (46 h infusion) in accordance with Dutch guidelines for systemic therapy of patients with metastatic colorectal cancer. HAIP was administered up to 6 months in case of complete resection of CRLMs or up to hepatic disease progression in patients who did not convert to surgery but without extrahepatic metastases. In patients with limited extrahepatic progression HAIP could be continued if consensus was obtained in the MDT meeting. Systemic therapy was administered according to standard clinical practice. After inclusion of nine patients, start doses of systemic therapy were adapted because signs of early liver toxicity were seen. Irinotecan dose was lowered to 150 mg/m^2 and fluorouracil to 2000 mg/m^2. Systemic dose reductions at the start and during treatment were allowed according to standard clinical practice. According to MSKCC protocol, predefined FUDR dose alterations were based on aspartate transferase, alkaline phosphatase or total bilirubin elevation, and in case of severe abdominal or gastric pain.

Treatment and response evaluations

Every 2 months, treatment response was evaluated with thoracic and abdominal CT according to RECIST criteria (version 1.1)[18]. Disease status and treatment were discussed in an MDT meeting.

Clinical data

Patient characteristics included age, sex, and American Society of Anesthesiologists (ASA) status. Tumour characteristics included primary tumour location (International Classification of Diseases for Oncology); mutational status; Tumour-, Node- and Metastasis status (TNM); the number and distribution of CRLMs; the maximum diameter of the largest CRLM; moment of CRLM diagnosis; and the FONG clinical risk score[19–22]. Treatment

characteristics related to surgery included surgical resections; operative time, blood loss, postoperative hospital admittance duration, 90-day postoperative Clavien–Dindo surgical complication score grade ≥3, and grade ≥3 pump device-related complications according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0)[23,24]. HAIP-SYS treatment characteristics included prior systemic therapy; type of systemic therapy, days from surgery to start HAIP and systemic therapy separately, number of systemic therapy cycles, and toxicity of HAIP and/or systemic therapy grade ≥3 (CTCAE)[24]. Radiological data were obtained before inclusion, before start HAIP-SYS in case of last imaging older than 6 weeks prior to aimed start, and every response evaluation. Patients were asked to complete health-related quality of life (QOL) forms at study inclusion, following surgery and at first radiological response evaluation. These assessed fatigue, nausea and vomiting, pain, physical functioning and global health score as assessed with the EORTC QLQ-C30 questionnaire and the overall health score assessed with the EQ-5D-3L questionnaire[25,26].

Outcomes

Primary outcome was feasibility, determined as the percentage of patients completing two cycles of HAIP combined with systemic therapy. Primary secondary outcome was safety, defined as surgical- and device-related complications and HAIP-SYS related toxicity. Other secondary outcomes were tumour response rates and QOL scores. Secondary outcomes were collected up to 6 months after HAIP implantation.

Statistics

A sample size of 31 patients would achieve 80.7% power with a target statistical significance of 0.05 to conclude feasibility in at least 70% of patients, against a null hypothesis of 90%. Frequencies (percentage) and median values (i.q.r.) were used for descriptions of categorical and continuous variables respectively. QOL scores were presented as means and compared between baseline and separate follow-up moments using a linear mixed model. All statistical analyses were performed in SPSS® version 29.0 (IBM Corp. Armonk, New York, USA), $P < 0.050$ was considered statistically significant.

Results

Between September 2020 and November 2022, 31 patients were included. Baseline characteristics are described in *Table 1*. Twenty-six patients (84%) had synchronous metastases and all patients had bilobar distribution of CRLMs with a median number of 13 CRLMs (i.q.r. 6–23). The primary tumour was *in situ* prior to study treatment in 24 patients (77%). Twelve patients (42%) had received prior systemic therapy within 6 months of CRLM diagnosis. Twenty-five patients had unresectable CRLMs and received induction HAIP-SYS; six patients had borderline-resectable CRLMs and received neoadjuvant HAIP-SYS.

Table 1 Baseline characteristics

	Total cohort $n = 31$	
Age at study inclusion in years, median (i.q.r.)	55	(49–64)
Sex, (M : F)	20:11	
ASA, *n* (%)		
1	8	(25.8)
2	21	(67.7)
3	2	(6.5)
Primary tumour location*, *n* (%)		
Right colon (cecum—transverse colon)	12	(38.7)
Left colon (splenic flexure—sigmoid)	16	(51.6)
Rectum	3	(9.7)
T-stage†, *n* (%)		
T0–2	4	(12.9)
T3–4	27	(87.1)
N stage†, *n* (%)		
N0	6	(19.4)
N1	11	(35.5)
N2	14	(45.2)
***RAS/RAF* mutation status, *n* (%)**		
RAS mutation	14	(48.3)
BRAF mutation	3	(10.3)
RAS/BRAF wild-type	12	(41.4)
Not available#	2	
CRLM diagnosis, synchronous‡, *n* (%)	26	(83.9)
CRLM number at diagnosis, median (i.q.r.)	13	(6–23)
CRLM distribution, bilobar, *n* (%)	31	(100)
CRLM size largest (mm), median (i.q.r.)	42	(19–66)
FONG clinical risk score§, *n* (%)		
0	0	(0)
1	1	(3.2)
2	3	(9.7)
3	15	(48.4)
4	10	(32.3)
5	2	(6.5)
Prior systemic therapy, *n* (%)	12	(38.7)
CAPOX (adjuvant), <6 months before CRLMs diagnosis	1	(8.3)
CAPOX-bevacizumab	7	(58.3)
FOLFOX-panitumumab and FOLFIRI-bevacizumab	1	(8.3)
FOLFOXIRI-bevacizumab	3	(25.0)

*According to the International Classification of Diseases for Oncology (ICD-O). †Including pretreated ((chemo)therapy and/or radiotherapy) colorectal cancer. T and N stage based on histopathological assessment. ‡Within 6 months of primary tumour diagnosis. §Score for predicting recurrence after hepatic resection for metastatic colorectal cancer. #Not included in statistical analysis. CRLM(s) = colorectal liver metastases; CAPOX = capecitabine and oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI = 5-fluorouracil, leucovorin and irinotecan; FOLFOXIRI = 5-fluorouracil, leucovorin, oxaliplatin and irinotecan.

Pump implantation

Pump implantation details are described in *Table 2*. All patients underwent laparotomy. The pump was implanted in 30 patients (97%). One patient did not receive a pump due to extrahepatic disease (extraregional lymph node metastases) found at laparotomy. In 22 of 30 patients (73%) the primary tumour was resected during laparotomy. Of these, 19 patients had a primary anastomosis. One patient had acute bowel obstruction symptoms 17 days after study inclusion, requiring immediate primary tumour resection (primary anastomosis). In this case the pump implantation was performed as scheduled 9 days after primary tumour surgery.

Primary outcome: feasibility

Of 30 patients with pumps, 29 started HAIP-SYS. One patient did not start HAIP-SYS because the definitive histopathology of the primary rectosigmoid tumour was a squamous cell carcinoma, even though the pre-inclusion colonoscopic biopsy was characterized as poorly differentiated adenocarcinoma. All 29 patients eligible to start HAIP-SYS started within 6 weeks after surgery. Twenty-eight of 31 patients (90%) received at least two cycles of HAIP-SYS. One patient did not receive a second cycle of HAIP due to grade 3 toxicity (gamma-glutamyltransferase and alkaline phosphatase increase and anaemia with indication for

Table 2 Surgical details (pump implantation)

	Total cohort N = 31	
Procedure, *n* (%)		
Pump*,†	6	(19.4)
Pump* + first stage hepatic surgery	2	(6.5)
Pump* + (extended) right hemicolectomy	8	(25.8)
Pump* + left hemicolectomy	4	(12.9)
Pump* + sigmoid colectomy	4	(12.9)
Pump* + PME	6	(19.4)
Right hemicolectomy	1	(3.2)
Blood loss in ml, median (i.q.r.)	200	(150–300)
Operative time in minutes, median (i.q.r.)	196	(170–244)
Postoperative hospital stay, median (range)	6	(3–11)

*All patients with pump implantation had concomitant cholecystectomy. †Including 1 patient with colorectal cancer resection 9 days before due to acute obstruction symptoms. PME = partial mesorectal excision.

Table 3 Details pump and systemic therapy (HAIP-SYS) in patients who started HAIP-SYS

	Total cohort N = 29	
Systemic chemotherapy, *n* (%)		
FOLFOX	20	(69.0)
FOLFIRI	9	(31.0)
Days from pump implantation to start pump chemotherapy, median (i.q.r.)	21	(15–28)
Days from pump implantation to start systemic chemotherapy, median (i.q.r.)	30	(28–37.5)
Number of systemic chemotherapy cycles at end second cycle pump chemotherapy*, *n* (%)		
1	1	(3.4)
2	8	(27.6)
3	14	(48.3)
4	6	(20.7)

*In case of stopping HAIP after first cycle ($n = 1$), number of systemic chemotherapy courses until first response evaluation. FOLFOX = combined 5-fluorouracil, leucovorin and oxaliplatin intravenous chemotherapy; FOLFIRI = combined 5-fluorouracil, leucovorin and irinotecan intravenous chemotherapy.

erythrocyte transfusion) after the first cycle of HAIP. The subsequent first response evaluation in this patient showed progression of CRLMs and extrahepatic metastases, resulting in discontinuation of HAIP-SYS. *Table 3* describes chemotherapy administration details.

Secondary outcomes

Safety

In the first two cycles of HAIP-SYS, 14 patients (45%) experienced a total of 21 grade ≥3 complications related to surgery, pump and/or chemotherapy (*Table 4*). Four of 31 patients (13%) had pump surgery-related complications, one of 29 patients had a pump dysfunction during HAIP-SYS, and 11 of 29 patients (38%) experienced chemotherapy toxicity mainly caused by liver enzyme elevation and nausea. All surgical- and pump device-related complications were resolved. Anastomotic leakage and extrahepatic perfusion or incomplete perfusion were not observed. There was no treatment-related mortality.

Table 4 Complications and toxicities of grade ≥3 during first two cycles HAIP combined with systemic therapy

Case	Complication	Grade	Treatment
	Surgery-related (Clavien–Dindo), 90-day postoperative 31 patients total		
1	Abscess liver	IIIa	Percutaneous drainage abscess + IV AB
2	Intra-abdominal abscess	IIIa	Percutaneous drainage abscess + IV AB
3	Catheter dislodgement/ haematoma, pump pocket	IIIb	Surgical haematoma removal and catheter reinsertion
4	Wound dehiscence, pump pocket	IIIb	Surgical replacement pump
	Pump device-related (CTCAE)		
	29 patients total		
5	HAIP dysfunction, decreasing flow rate	III	Surgical replacement pump (during first stage hepatectomy, 5 months postoperative)
	Chemotherapy-related (CTCAE), FUDR C1D1 up to end second cycle*		
	29 patients total		
6	ALAT + GGT increase	IV + III	Start pump dexamethasone C2D15 + delay SYS C3†
7	ASAT + GGT increase	III	Start pump dexamethasone C2D15 + delay SYS C3
8	GGT increase	III	Start pump dexamethasone C1D15 + start SYS C1 75%
8	ALP increase	III	Continue pump dexamethasone + delay SYS C3
8	Anaemia	III	Erythrocyte transfusion + delay SYS C3
9	Anaemia	III	Erythrocyte transfusion + start SYS C1 OX 75%
10	Vascular access complication (deep vein thrombus upper arm at PICC site)	III	PICC removal + start oral anticoagulant
11	Thromboembolic event (pulmonary embolism)	III	Hospitalization: start oral anticoagulant + delay SYS C4
12	Typhlitis	III	Hospitalization: IV AB + fluids + delay SYS C4
13	ALAT increase	III	Start pump dexamethasone C2D15 + delay SYST C3
14	Nausea	III	Hospitalization: IV fluids + delay SYS C5
1	Nausea	III	Hospitalization: IV fluids (combined with liver abscess)
1	Hypokalaemia	III	Normal diet (during hospitalization nausea + liver abscess)
1	GGT increase	III	Continue delay SYS C2

*In case of delay beyond first response evaluation ($n = 1$) or stop after first cycle ($n = 1$), toxicity until first response evaluation. †SYS not restarted after conversion surgery. AB = antibiotics; ALAT = alanine transaminase; ALP = alkaline phosphatase; ASAT = aspartate aminotransferase; C = chemotherapy cycle; CTCAE = Common Terminology Criteria for Adverse Events version 5.0; C = cycle number; D = day of cycle; GGT = gamma-glutamyltransferase; HAIP = hepatic arterial infusion pump; IV = intravenous; OX = oxaliplatin; PICC = peripherally inserted central catheter; SYS = systemic chemotherapy (FOLFOX/FOLFIRI).

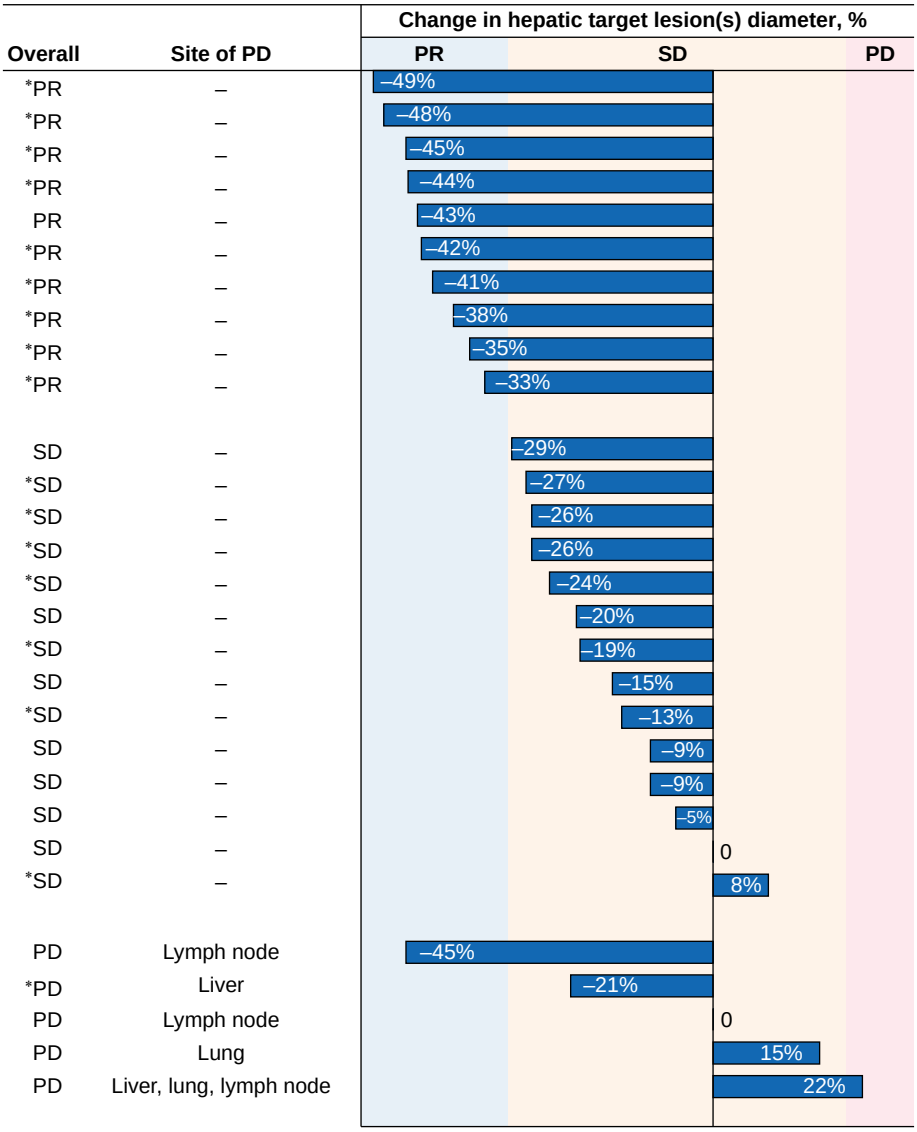

Fig. 1 Radiological first response after two cycles of HAIP-SYS (*n* = 29†)

HAIP-SYS = combined chemopump and systemic therapy; PD = progressive disease; PR = partial response, SD = stable disease. *Chemo-naive patients. †Two patients did not start HAIP-SYS and are not included, one patient received only one cycle of HAIP-SYS.

Subsequent severe toxicity of HAIP-SYS up to 6 months is provided in *Table S2*. No additional pump-related complications were observed. Hepatic artery thrombosis, bleeding or biliary sclerosis did not occur within 6 months. A median number of 4 FUDR cycles (i.q.r. 3–4.5) and 7 SYS cycles (i.q.r. 4.5–9) were administered.

Response rates

Figure 1 shows the first radiological response rates of all 29 patients who started HAIP-SYS. Median time from start HAIP to first response evaluation was 7 weeks (i.q.r. 6–7). Ten patients (34%) had partial response, 14 patients (48%) had stable disease and 5 patients (17%) had progressive disease. Disease control rate was 83% (24/29 patients) and hepatic disease control rate was 93% (27/29 patients).

Within 6 months post HAIP implantation one additional patient had progressive disease. Sixteen (55.2%) patients had partial response and seven (24.1%) had stable disease. Nine of 29 patients underwent either complete conversion surgery during the first 6 months or the first stage procedure of conversion surgery.

Quality of life

Twenty-eight patients completed 69 questionnaires. *Figure 2* shows the QOL scores per evaluation moment. The largest effect on QOL was seen following surgery. Fatigue was higher at both follow-up moments compared to baseline. No significant differences were observed regarding nausea and vomiting scores over time. All other scores were lower following surgery (first follow-up evaluation) compared to baseline but returned to baseline scores at first radiological response evaluation (second follow-up evaluation).

Discussion

This prospective study showed that combined HAIP-SYS for patients with unresectable or borderline-resectable CRLMs was feasible in the Netherlands. Surgical complications of pump

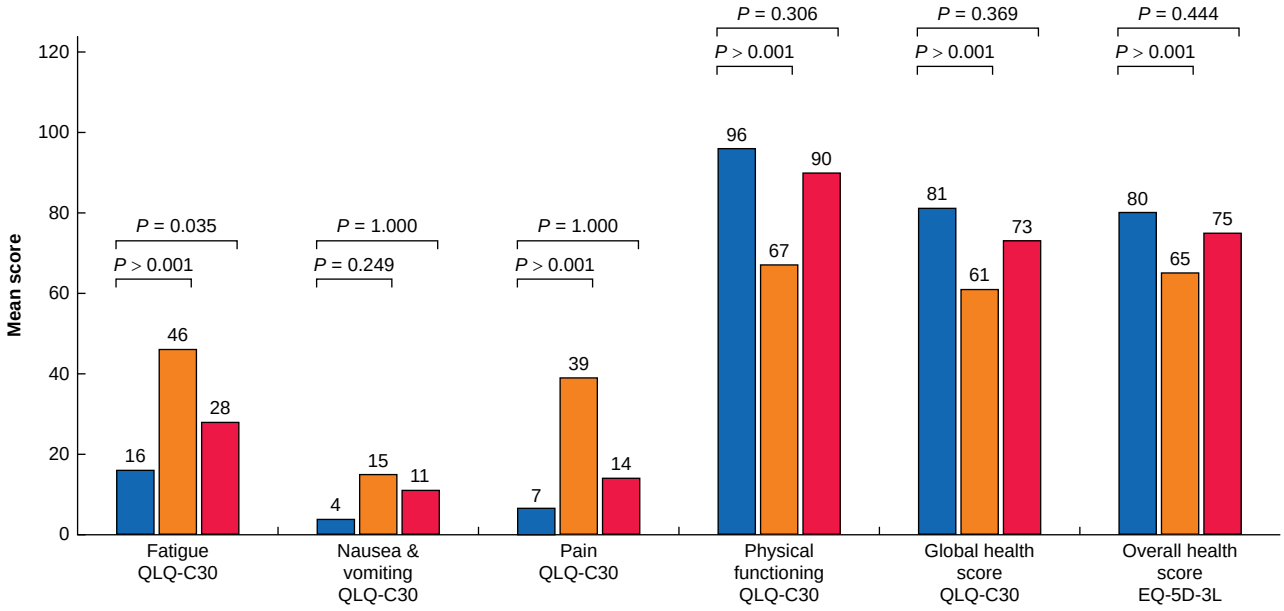

Fig. 2 Quality of life scores per evaluation moment.

Blue column = baseline; orange column = postoperative; red column = first response evaluation.

placement and primary tumour resection, if still *in situ*, and toxicity of the first two cycles of HAIP-SYS were deemed acceptable. Whether HAIP-SYS also leads to increased conversion rates and survival benefit in the Dutch setting needs to be explored.

Until recently, Dutch patients with unresectable liver-only CRLMs were enrolled in the CAIRO5 study investigating the optimal neoadjuvant systemic therapy regimen[3]. A successive nationwide phase III study, the multicentre RCT PUMP-IT study, has been designed for chemo-naive patients with unresectable CRLMs. Standard of care (optimal induction systemic treatment based on progression-free survival (PFS) and OS outcomes of the CAIRO5 study) will be compared to HAIP-SYS. As in CAIRO5, resectability of metastases will be determined by a central panel. Overall survival will be the primary outcome. This trial was recently funded by the Dutch Cancer Society and will be launched in 2024 (EUDRA CT 2023-506194-35-00). In the USA the EA2222 'PUMP' trial will start to enrol patients in 2024. In this study, patients with unresectable liver metastases who previously had first-line chemotherapy will be randomized to HAIP-SYS or systemic treatment (clinicaltrials.gov: NCT05863195).

The results of this study echo the experiences published by the MSKCC team for this group of patients with extensive metastases confined to the liver. MSKCC reported complications grade ≥3 directly related to the pump (implantation) in 13% of patients (total cohort $n = 373$, 29% prior systemic therapy) treated in 2000–2009[8]. Two patients (0.2%) died within 90 days following surgery due to complications. Overall, 12 patients (3%) never received HAIP-SYS due to complications. In a previous cohort (1986–2001), a 22% pump-related complication rate was reported, most commonly related to the arterial system (51%, 62 of 120 patients)[27]. Observed complications such as arterial thrombosis ($n = 33$), extrahepatic perfusion ($n = 12$) and catheter-related complications ($n = 33$) were not observed in the current study. Liver enzyme elevations (grade ≥3) were observed in 20% of patients and the best response rate during HAIP-SYS was 73–92% for combined chemo-naive patients and patients who received one or more lines of systemic therapy ($n = 64$, 67% prior SYS; $n = 49$, 53% prior SYS)[5,6]. The data of 56 chemo-naive patients treated at MSKCC since 2003 were recently updated[12]. Of these patients, 5% experienced grade 3 primary tumour and HAIP surgery complications, 24% had liver enzyme toxicity grades 3–4 and 79% showed response to therapy at 2 months after HAIP-SYS initiation. In the current study the observed intervals between HAIP implantation and start of HAIP and systemic therapy respectively were rather similar with the MSKCC experience[6,7,12].

A phase II study of HAIP combined with systemic therapy was necessary before an RCT could be initiated in the Netherlands, despite multiple MSKCC publications, successful new HAIP programmes in Northern America with former MSKCC physicians and a successful pilot study for adjuvant HAIP outside the USA[9,13–16]. In the EU and the Netherlands in particular there was no experience with this combined treatment. The safety profile was also unknown or limited; for example, of HAIP implantation in this patient category with extensive metastases, of concomitant primary tumour resection and of concomitant systemic therapy. This study proved feasibility. Systemic therapy was initially dosed according to standard Dutch regimens, but due to early hepatic toxicity, dosages were lowered to MSKCC dosages. Severe biliary sclerosis, a common HAIP toxicity, was not observed within the first 6 months after pump implantation[5]. However, this may occur later during or even after treatment[16].

In this study, primary tumour resection was performed at laparotomy for pump implantation. This has been controversial. Short-term results of the CAIRO4 trial showed increased early mortality among patients with unresectable metastatic disease who underwent primary tumour resection as compared with patients who started directly with systemic therapy[28]. These patients, however, more often had multi-organ disease and comprise a different population with more advanced disease than the population in this study with liver-only metastases. Several reasons to perform primary tumour resection in the setting of HAIP therapy included the assumed higher chance of conversion to resectable disease and the opportunity to continue HAIP only to control CRLMs when systemic toxicity

was encountered[5]. MSKCC results of primary tumour resection at the time of pump implantation are discordant with the results of the CAIRO4 study[28,29]. Primary tumour resection was observed to be generally safe. However, more complications occurred in patients who underwent concomitant stoma reversal[29].

Limitations of the current study include the sample size, which does not allow conclusions on survival to be drawn. The sample was sufficient to establish feasibility, but the study was not powered to address oncological benefit. Although the short-term safety profile was good, long-term data on biliary sclerosis and safety of conversion surgery after HAIP-SYS have to be awaited. Data on conversion to resection rates, pathology response and survival are not mature yet.

Author contributions

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Disclosures

The authors have no conflict of interests related to this publication.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data that support the findings of this study are available from the corresponding author, K.F.D. Kuhlmann, upon reasonable request.

References

1. Meyer YM, Olthof PB, Grünhagen DJ, Swijnenburg RJ, Elferink MAG, Verhoef C. Interregional practice variations in the use of local therapy for synchronous colorectal liver metastases in The Netherlands. *HPB (Oxford)* 2022;**24**:1651–1658
2. Meyer Y, Olthof PB, Grünhagen DJ, de Hingh I, de Wilt JHW, Verhoef C *et al.* Treatment of metachronous colorectal cancer metastases in The Netherlands: a population-based study. *Eur J Surg Oncol* 2022;**48**:1104–1109
3. Bond MJG, Bolhuis K, Loosveld OJL, de Groot JWB, Droogendijk H, Helgason HH *et al.* First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. *Lancet Oncol* 2023;**24**:757–771
4. Anteby R, Kemeny NE, Kingham TP, D'Angelica MI, Wei AC, Balachandran VP *et al.* Getting chemotherapy directly to the liver: the historical evolution of hepatic artery chemotherapy. *J Am Coll Surg* 2021;**232**:332–338
5. Pak LM, Kemeny NE, Capanu M, Chou JF, Boucher T, Cercek A *et al.* Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: long term results and curative potential. *J Surg Oncol* 2018;**117**:634–643
6. Kemeny NE, Melendez FD, Capanu M, Paty PB, Fong Y, Schwartz LH *et al.* Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2009;**27**:3465–3471
7. Kemeny N, Jarnagin W, Paty P, Gönen M, Schwartz L, Morse M *et al.* Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. *J Clin Oncol* 2005;**23**:4888–4896
8. Ammori JB, Kemeny NE, Fong Y, Cercek A, Dematteo RP, Allen PJ *et al.* Conversion to complete resection and/or ablation using hepatic artery infusional chemotherapy in patients with

unresectable liver metastases from colorectal cancer: a decade of experience at a single institution. *Ann Surg Oncol* 2013;**20**: 2901–2907
9. Muaddi HA-O, D'Angelica M, Wiseman JA-O, Dillhoff M, Latchana N, Roke R *et al.* Safety and feasibility of initiating a hepatic artery infusion pump chemotherapy program for unresectable colorectal liver metastases: a multicenter, retrospective cohort study. *J Surg Oncol* 2021;**123**:252–260. doi: 10.1002/jso.26270
10. Kemeny N, Daly J, Oderman P, Shike M, Chun H, Petroni G *et al.* Hepatic artery pump infusion: toxicity and results in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1984;**2**:595–600
11. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983;**10**:176–182
12. Verheij FS, Kuhlmann KFD, Silliman DR, Soares KC, Kingham TP, Balachandran VP *et al.* Combined hepatic artery infusion pump and systemic chemotherapy in the modern era for chemotherapy-naive patients with unresectable colorectal liver metastases. *Ann Surg Oncol* 2023;**30**:8014–8015
13. Chakedis J, Beal EW, Sun S, Galo J, Chafitz A, Davidson G *et al.* Implementation and early outcomes for a surgeon-directed hepatic arterial infusion pump program for colorectal liver metastases. *J Surg Oncol* 2018;**118**:1065–1073
14. Creasy JM, Napier KJ, Reed SA, Zani S Jr, Wong TZ, Kim CY *et al.* Implementation of a hepatic artery infusion program: initial patient selection and perioperative outcomes of concurrent hepatic artery infusion and systemic chemotherapy for colorectal liver metastases. *Ann Surg Oncol* 2020;**27**:5086–5095
15. Walker BA-O, Billingsley KG, Sutton TA-O, Kolbeck KJ, Korngold EK, Nabavizadeh N *et al.* Hepatic arterial infusion pump chemotherapy combined with systemic therapy for patients with advanced colorectal liver metastases: outcomes in a newly established program. *J Surg Oncol* 2022;**126**:513–522. doi: 10.1002/jso.26911
16. Buisman FE, Grünhagen DJ, Homs MYV, Grootscholten C, Filipe WF, Kemeny NE *et al.* Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases: results of a safety and feasibility study in The Netherlands. *Ann Surg Oncol* 2019;**26**:4599–4607
17. Isoniemi H, Uutela A, Nordin A, Lantto E, Kellokumpu I, Ovissi A *et al.* Centralized repeated resectability assessment of patients with colorectal liver metastases during first-line treatment: prospective study. *Br J Surg* 2021;**108**:817–825
18. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S *et al.* RECIST 1.1—Update and clarification: from the RECIST committee. *Eur J Cancer* 2016;**62**:132–137. doi:10.1016/j.ejca.2016.03.081
19. Fritz A, World Health Organization. Topography C18-20. In: Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S (eds.), *International Classification of Diseases for Oncology (3rd edn, first revision)*. Geneva: World Health Organization, 2013, 36
20. Siriwardena AA-O, Serrablo A, Fretland ÅA, Wigmore SJ, Ramia-Angel JA-O, Malik HZ *et al.* Multisocietal European consensus on the terminology, diagnosis, and management of patients with synchronous colorectal cancer and liver metastases: an E-AHPBA consensus in partnership with ESSO, ESCP, ESGAR, and CIRSE. *Br J Surg* 2023;**110**:1161–1170
21. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;**230**:309–318; discussion 18–21
22. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours (8th edn)*. Oxford: Wiley Blackwell, 2016
23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–213
24. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (cancer.gov; accessed 6 April 2024)
25. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al.* The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**:365–376
26. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;**33**:337–343
27. Allen PJ, Nissan A, Picon AI, Kemeny N, Dudrick P, Ben-Porat L *et al.* Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg* 2005;**201**:57–65
28. van der Kruijssen DEW, Elias SG, Vink GR, van Rooijen KL, 't Lam-Boer J, Mol L *et al.* Sixty-day mortality of patients with metastatic colorectal cancer randomized to systemic treatment vs primary tumor resection followed by systemic treatment: the CAIRO4 phase 3 randomized clinical trial. *JAMA Surg* 2021;**156**:1093–1101
29. Verheij FS, Soares KC, Beets GL, Kok NFM, Yuval JB, Kemeny NE *et al.* Timing of primary tumor resection in synchronous metastatic colon cancer patients undergoing hepatic arterial infusion pump placement. *Ann Surg Oncol* 2022;**29**:2044–2051