https://doi.org/10.1016/j.hpb.2024.03.1158

ORIGINAL ARTICLE

Extrahepatic perfusion and incomplete hepatic perfusion after hepatic arterial infusion pump implantation: incidence and clinical implications

Wills F. Filipe[1], Florian E. Buisman[1], Stijn Franssen[1], Myrtle F. Krul[2], Dirk J. Grünhagen[1], Roel J. Bennink[3], Karen Bolhuis[4], Rutger C.G. Bruijnen[5], Tineke E. Buffart[6], Mark C. Burgmans[7], Otto M. van Delden[3], Pascal G. Doornebosch[8], Paul D. Gobardhan[9], Laura Graven[10], Jan Willem B. de Groot[11], Cecile Grootscholten[4], Jeroen Hagendoorn[12], Paul Harmsen[1], Marjolein Y.V. Homs[13], Elizabeth G. Klompenhouwer[14], Niels F.M. Kok[2], Marnix G.E.H. Lam[15], Olaf J.L. Loosveld[16], Mark A.J. Meier[17], J. Sven D. Mieog[18], Ad H.J. Oostdijk[17], Loubna Outmani[1], Gijs A. Patijn[19], Stefan Pool[20], Daphne D.D. Rietbergen[6], Jeanine M.L. Roodhart[21], Frank M. Speetjens[22], Rutger Jan Swijnenburg[23], Michelle W.J. Versleijen[24], Cornelis Verhoef[1], Koert F.D. Kuhlmann[2], Adriaan Moelker[10,a], Bas Groot Koerkamp[1,a] Dutch HAIP consortium

[1]Department of Surgery, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, [2]Department of Surgery, The Netherlands Cancer Institute, Amsterdam, [3]Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Rotterdam, [4]Department of Medical Oncology, The Netherlands Cancer Center, Amsterdam, [5]Department of Radiology, University Medical Center Utrecht, Utrecht, [6]Department of Medical Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, [7]Department of Radiology and Nuclear Medicine, Leiden University Medical Center, Leiden, [8]Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, [9]Department of Surgery, Amphia Hospital, Breda, [10]Department of Radiology and Nuclear Medicine, Erasmus MC, Erasmus University, Rotterdam, [11]Department of Medical Oncology, Isala, Zwolle, [12]Department of Surgery, University Medical Center Utrecht, Utrecht, [13]Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, [14]Department of Radiology, The Netherlands Cancer Institute, Amsterdam, [15]Department of Nuclear Medicine, University Medical Center Utrecht, Utrecht, [16]Department of Medical Oncology, Amphia Hospital, Breda, [17]Department of Radiology and Nuclear Medicine, Isala, Zwolle, [18]Department of Surgery, Leiden University Medical Center, Leiden, [19]Department of Surgery, Isala, Zwolle, [20]Department of Radiology and Nuclear Medicine, Amphia Hospital, Breda, [21]Department of Medical Oncology, University Medical Center Utrecht, Utrecht, [22]Department of Medical Oncology, Leiden University Medical Center, Leiden, [23]Department of Surgery, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, and [24]Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, the Netherlands

Abstract

Introduction: This study investigates the incidence of extrahepatic perfusion and incomplete hepatic perfusion at intraoperative methylene blue testing and on postoperative nuclear imaging in patients undergoing hepatic arterial infusion pump (HAIP) chemotherapy.

Methods: The first 150 consecutive patients who underwent pump implantation in the Netherlands were included. All patients underwent surgical pump implantation with the catheter in the gastroduodenal artery. All patients underwent intraoperative methylene blue testing and postoperative nuclear imaging (^{99m}Tc-Macroaggregated albumin SPECT/CT) to determine perfusion via the pump.

Results: Patients were included between January-2018 and December-2021 across eight centers. During methylene blue testing, 29.3% had extrahepatic perfusion, all successfully managed intraoperatively. On nuclear imaging, no clinically relevant extrahepatic perfusion was detected (0%, 95%CI: 0.0–2.5%). During methylene blue testing, 2.0% had unresolved incomplete hepatic perfusion. On postoperative nuclear imaging, 8.1% had incomplete hepatic perfusion, leading to embolization in only 1.3%.

Conclusion: Methylene blue testing during pump placement for intra-arterial chemotherapy identified extrahepatic perfusion in 29.3% of patients, but could be resolved intraoperatively in all patients. Postoperative nuclear imaging found no clinically relevant extrahepatic perfusion and led to embolization in only 1.3% of patients. The role of routine nuclear imaging after HAIP implantation should be studied in a larger cohort.

Received 8 September 2023; accepted 17 March 2024

[a] Shared senior authors.

Correspondence
Wills Filipe, Department of Surgery, Erasmus MC Cancer Institute, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. E-mail: w.filipe@erasmusmc.nl (W.F. Filipe)

Correspondence
Bas Groot Koerkamp, Department of Surgery, Erasmus MC Cancer Institute, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. E-mail: b.grootkoerkamp@erasmusmc.nl (B. Groot Koerkamp)

Introduction

Hepatic arterial infusion pump (HAIP) chemotherapy with floxuridine has been investigated in Memorial Sloan Kettering Cancer Center (MSKCC) as a treatment for patients with colorectal liver metastases (CRLM) and intrahepatic cholangiocarcinoma (iCCA).[1,2] Since 2018, HAIP chemotherapy has been studied in the Netherlands in several clinical trials.

HAIP chemotherapy involves continuous administration of chemotherapy directly in the hepatic artery. The rationale for hepatic intra-arterial administration is that, in contrast to liver parenchyma, the blood supply of liver tumors is predominantly derived from the hepatic artery rather than the portal vein 3. Moreover, the chemotherapeutic agent floxuridine has a first-pass extraction in the liver as high as 95%,[4] allowing for high dosage in the liver with negligible systemic exposure.[5]

However, this high dosage can lead to local toxicity if extrahepatic structures (i.e., the stomach, duodenum, or pancreas) are perfused with floxuridine.[6] Extrahepatic perfusion is caused by small arterial branches of the left and right hepatic artery that run back to the stomach, duodenum, and pancreas or due to arteriovenous shunting. Extrahepatic perfusion has been reported in 6% of patients,[7] resulting in gastroduodenal ulcers and pancreatitis.[6,8–10] Incomplete hepatic perfusion occurs when floxuridine does not reach all liver segments. Incomplete hepatic perfusion could lead to disease progression in the non-perfused liver segments. It is explained by arterial blood flow to the liver that is not infused with floxuridine, due to aberrant and accessory hepatic arteries, or adrenal and diaphragmatic arteries feeding liver tumors.

To prevent extrahepatic perfusion, the hepatic artery (common and proper) and the gastroduodenal artery (GDA) are circumferentially skeletonized during HAIP implantation.[11] Incomplete hepatic perfusion is avoided by transecting or ligating any artery that feeds the liver and is not infused with floxuridine.[10,12]

During surgery, methylene blue is injected in the bolus port of the implanted pump in order to detect extrahepatic perfusion or incomplete hepatic perfusion. Additional transection and/or ligation is performed of branches responsible for extrahepatic perfusion and incomplete hepatic perfusion with methylene blue. Postoperatively, extrahepatic perfusion and incomplete hepatic perfusion is also assessed with nuclear imaging (i.e., ^{99}Tc-labeled macroaggregated albumin (MAA) SPECT/CT imaging) injected via the pump bolus port to rule out extrahepatic perfusion before starting HAIP chemotherapy. Extrahepatic perfusion and incomplete hepatic perfusion may be resolved postoperatively by endovascular embolization of responsible arteries.

The aim of this study was to investigate the incidence and clinical implications of extrahepatic perfusion and incomplete hepatic perfusion found during intraoperative methylene blue testing or on postoperative nuclear imaging in patients treated with HAIP chemotherapy.

Methods

Study design

A multicenter prospective observational study was performed including the first 150 consecutive patients in five clinical trials in the Netherlands (PUMP-pilot,[13,14] PUMP-1,[15,16] PUMP-2,[17] PUMP-3[18]; and PUMP-IT[19]) or a compassionate use program. Inclusion criteria of the individual trials can be found in the trials' study protocols. The surgical procedures were performed in 8 hospitals. All studies were approved by the medical ethics board and all patients signed informed consent. The present study is a retrospective analysis of these prospective trials.

Preoperative radiological evaluation

Preoperative imaging consisted of an arterial phase CT angiography with 1 mm slide thickness according to study protocol. This was performed to determine feasibility of HAIP catheter placement in the Gastroduodenal artery (GDA) and identify aberrant and accessory hepatic arteries preoperatively.

Perioperative procedures

During surgery, the common and proper hepatic artery, as well as the GDA were dissected circumferentially. Any side branches to extrahepatic structures, including the right gastric artery were ligated and divided. The teres hepatis ligament, falciform ligament, and lesser omentum were transected to further prevent extrahepatic perfusion. Accessory and replaced hepatic arteries were ligated, such that the liver would be perfused only by the proper hepatic artery containing floxuridine infused from the GDA. Intrahepatic shunts allow for cross-perfusion after transecting replaced or accessory hepatic arteries. In addition, a cholecystectomy was performed to prevent floxuridine induced cholecystitis.[20] The GDA was ligated as distal from the hepatic artery as possible and a transverse arteriotomy was performed to insert the HAIP catheter up to, but not beyond, the bifurcation with the hepatic artery. A catheter protruding into the common hepatic artery causes turbulent blood flow that may result in arterial thrombosis. Failure to pass the tip of the catheter up to the hepatic artery leaves a short segment of the GDA exposed to full concentrations of floxuridine without the diluting effect of blood flow, potentially resulting in pseudo−aneurysm formation or catheter dislodgment with hemorrhage. The catheter was secured into the GDA by four non-absorbable 2.0 ties (e.g., silk or mersilene) proximal to the tying beads.

Subcutaneous implantation of the HAIP with a constant non-programmable flow rate (Tricumed IP2000 V) was performed preferentially in the lower left quadrant in the abdomen. After securing the catheter in the GDA, up to 10 ml of 10 mg/ml methylene blue was infused directly into the hepatic artery via the bolus port of the pump. The methylene blue was injected slowly to avoid retrograde flow in the common hepatic artery that may result in false positive extrahepatic perfusion. Spots of blue forming outside the liver were identified and responsible branches were ligated. The initial methylene blue bolus should be small (1−3 cc) so that it can be repeated after additional dissection until absence of extrahepatic perfusion and incomplete hepatic perfusion is confirmed at the end of the test. Pump implantation was combined with partial hepatectomy in patients with resectable CRLM.

Postoperative imaging

Prior to the first administration of HAIP floxuridine, additional imaging was performed to confirm absence of extrahepatic perfusion and incomplete hepatic perfusion. An interventional radiologist accessed the bolus port of the infusion pump with a needle under X-ray guidance. A digital subtraction angiography (DSA) was performed by careful manual injection of contrast agent (e.g., Iomeron 300) via the separate bolus port of the Tricumed pump to confirm the positioning of the needle before nuclear imaging. Moreover, the DSA allowed to rule out leakage at the pump-catheter and catheter-GDA connection and to rule out hepatic artery thrombosis, arterial dissection, and catheter occlusion (Fig. 1A). Subsequently, nuclear imaging (i.e., ^{99m}Tc-MAA SPECT/CT scan) was performed. The ^{99m}Tc-MAA (150 MBq) was administered through the accessed bolus port of the pump. Within 1 h after injection, a SPECT/CT scan was performed (Fig. 1B). Results were obtained and evaluated by experienced interventional radiologists and nuclear medicine physicians.

Patients with extrahepatic perfusion and/or incomplete hepatic perfusion on postoperative nuclear imaging were considered for embolization of any responsible arterial branches. Nuclear imaging was repeated after embolization prior to the first HAIP floxuridine treatment. Imaging (e.g., CT and/or nuclear imaging) was repeated whenever extrahepatic perfusion was clinically suspected during HAIP floxuridine treatment.

Chemotherapeutic regimen

A detailed description of the chemotherapeutic regimen is available in the study protocols.[16,21] In summary, the first cycle of HAIP floxuridine was initiated preferably 2−4 weeks after surgery depending on the patient's recovery after surgery and results from the postoperative nuclear imaging. The pump was refilled with a heparinized saline solution (35,000 IE in 35 mL NaCl 0.9%) every two weeks until the start of HAIP floxuridine to prevent thrombosis of the catheter. All patients were scheduled to receive at least six cycles of 4 weeks. Each cycle consisted of 2 weeks of HAIP chemotherapy with floxuridine followed by a 2-week rest period during which the pump was filled with the heparinized saline solution. Floxuridine was administered at 0.12 mg/kg/day.[14,16,22] A prophylactic dose of 20 mg of oral

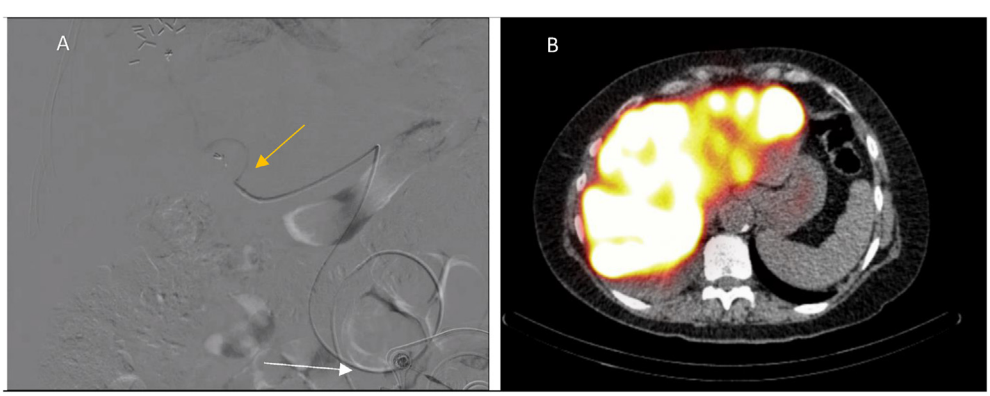

Figure 1 Normal postoperative imaging via the pump bolus port. A) Digital subtraction angiography via bolus port: no leakage from pump−catheter junction (white arrow) or catheter-GDA junction (yellow arrow), and no stasis of contrast in hepatic artery (suggestive of thrombosis or dissection). B) ^{99m}Tc-MAA imaging: Radioactivity detected in all segments of the liver. Heterogeneous distribution is a common finding.

proton pump inhibitors was prescribed daily during HAIP chemotherapy.

Training

The initial eight pump implantations were supervised by experienced surgeons from MSKCC (MD and TK). The multidisciplinary teams of the first two participating centers (Erasmus MC and the Netherlands Cancer Institute) visited MSKCC for a 2-day workshop. As the two first centers gained experience, the remaining 6 centers were trained by the first two centers, while the team in MSKCC was available for consultation at a distance. Newly participating centers performed the implantations independently when ready; this was dependent on volume and time interval of procedures.

During the whole study, A PhD student attended all implantations, supervised pump refills, provided hands-on workshops for nurses and staff members, and oversaw all postoperative procedures until the departments could perform them independently.

Definitions

Extrahepatic perfusion was defined as any observed extrahepatic blue staining during intraoperative methylene blue testing or extrahepatic radioactivity on postoperative nuclear imaging (i.e., ^{99m}Tc-MAA SPECT/CT). Incomplete hepatic perfusion was defined as absence of blue staining or uptake of radioactivity in one or more liver segments, excluding resected and ablated segments. The presence of extrahepatic perfusion and incomplete hepatic perfusion was collected retrospectively from the operative note and the report of the nuclear imaging. The incidence was defined as the number of new cases during the immediate 90-days postoperative period divided by the size of the population at the start of the time period. Major liver resection was defined as complete resection of 3 or more adjacent liver segments.

Statistical analysis

Continuous variables were presented as medians with interquartile range (IQR), and categorical variables as proportions with 95% confidence interval (CI). Difference in proportions between groups were calculate using chi-squared test. The 95% CIs for zero-incidence were calculated using the Wilson method.[23] All analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL) and R version 3.5.1 (http://www.r-project.org).

Table 1 Baseline characteristics (n = 150)

	n (%)
Female Sex	66 (44.0)
Age, median [IQR]	60 [54–69]
Center	
Center 1	64 (42.7)
Center 2	46 (30.7)
Center 3	9 (6.0)
Center 4	14 (9.3)
Center 5	9 (6.0)
Center 6	1 (0.7)
Center 7	6 (4.0)
Center 8	1 (0.7)
Clinical trial	
PUMP Pilot – adjuvant CRLM	30 (20.0)
PUMP-1: adjuvant CRLM	49 (32.7)
PUMP-2: unresectable iCCA	33 (22.0)
PUMP-IT: unresectable CRLM	17 (11.3)
PUMP-3: adjuvant for recurrent CRLM	19 (12.7)
Compassionate Use – (un)resectable CRLM	2 (1.3)
Indication for HAIP chemotherapy	
Initial resectable CRLM	80 (53.3)
Recurrent resectable CRLM	19 (12.7)
Unresectable iCCA	33 (22.0)
Unresectable CRLM	18 (12.0)
Hepatic artery anatomy	
Normal anatomy	98 (65.3)
Replaced LHA	10 (6.7)
Replaced RHA	21 (14.0)
Accessory LHA	9 (6.0)
Accessory RHA	3 (2.0)
Replaced RHA and accessory LHA	2 (1.3)
Aberrant CHA from SMA	3 (2.0)
Other	4 (2.7)
Previous liver resection or ablation	19 (12.7)
Surgery details	
HAIP implantation only	34 (22.7)
HAIP implantation with minor liver resection	104 (69.3)
HAIP implantation with major liver resection	12 (8.0)

CRLM: Colorectal liver metastases; HAIP: Hepatic Arterial Infusion Pump; iCCA: intrahepatic Cholangiocarcinoma; IQR: Interquartile Range; LGA: Left Gastric Artery; LHA: Left Hepatic Artery; RHA; Right Hepatic Artery; SMA: Superior Mesenteric artery.

Results

Patient characteristics

A total of 150 consecutive patients underwent HAIP pump implantation for intra-arterial chemotherapy between January 2018 and December 2021. Baseline patient characteristics are summarized in Table 1. Ninety-nine patients (66.0%) had resectable CRLM, 18 patients (12.0%) had unresectable CRLM, and 33 patients (22.0%) had unresectable iCCA. Nineteen patients (12.7%) had previous local treatment (i.e., resection and/or thermal ablation) of the liver. Normal arterial anatomy was present in 98 patients (65.3%). Fifty-two patients (34.7%) had a replaced and/or accessory hepatic artery. Thirty-four patients (22.7%) underwent HAIP implantation without hepatectomy, 104 (69.3%) underwent HAIP implantation and a minor hepatectomy, and twelve patients (8.1%) underwent HAIP implantation and a major hepatectomy. The HAIP catheter was implanted in the GDA in 147 (98.0%) patients. In the remaining three patients (2.0%), the catheter was placed in the right gastric artery (n = 1), right hepatic artery (n = 1), or in the middle (i.e., segment 4) hepatic artery (n = 1).

The median follow-up was 16.5 (interquartile range: 11.4–30.8) months.

Extrahepatic perfusion

Table 2 presents the incidence of extrahepatic perfusion found during intraoperative methylene blue testing and on postoperative nuclear imaging. The intraoperative initial methylene blue test showed extrahepatic perfusion in 44 (29.3%) patients, most commonly in the duodenum (n = 16, 10.7%) and/or pancreas (n = 12, 8.0%). The branches giving rise to the extrahepatic perfusion were identified and ligated in all patients. During the final intraoperative methylene blue testing, extrahepatic perfusion had been resolved in all patients.

Table 2 Extrahepatic perfusion during intraoperative methylene blue testing and on postoperative nuclear imaging

Outcome	n (%)	Postoperative Embolization
Extrahepatic perfusion at first methylene blue test (n = 150)	***44 (29.3)***	–
Duodenum	16 (10.7)	–
Pancreas	12 (8.0)	–
Common bile duct	4 (2.7)	–
Free intra-abdominal leakage	2 (1.0)	–
Portocaval lymph node	2 (1.0)	–
Stomach	1 (0.7)	–
Diaphragm	1 (0.7)	–
Lesser omentum	1 (0.7)	–
Unknown location	5 (3.3)	–
Extrahepatic perfusion at final methylene blue test (n = 150)	***0***	-
Extrahepatic perfusion at nuclear imaging (n = 148)[a]	***2 (1.4)***	***None***
Stomach (physiological)	1 (0.7)	None
Common bile duct (physiological)	1 (0.7)	None

[a] Two patients did not undergo postoperative nuclear imaging; one patient had an unsalvageable hepatic artery dissection and did not undergo nuclear imaging, the other patient died before nuclear imaging was performed.

Postoperative nuclear imaging was performed in 148 patients (98.7%); one patient had an unsalvageable hepatic artery dissection and did not undergo nuclear imaging, the other patient died before nuclear imaging was performed. Postoperative nuclear imaging found apparent extrahepatic perfusion in two patients (1.3%); one at the common bile duct (Fig. 2A) and one in the wall of the stomach (Fig. 2B), despite a normal final methylene blue test. These findings were both considered as false positives; physiological arterial blood supply from the liver hilum to the common bile duct and physiological aggregation of free pertechnetate in the wall of the stomach. Both patients underwent HAIP floxuridine without developing symptoms or signs of extrahepatic exposure to floxuridine. Therefore, the incidence of clinically relevant extrahepatic perfusion found on routine postoperative nuclear imaging was 0.0% (95%CI: 0.0–2.5%).

Incomplete hepatic perfusion

Table 3 presents the incidence of incomplete perfusion found during intraoperative methylene blue testing and on postoperative nuclear imaging. Incomplete hepatic perfusion was observed intraoperatively during the methylene blue test in three patients (2.0%). The first patient had an early bifurcation of the proper hepatic artery at the GDA (i.e., trifurcation of the common hepatic artery) with preferential flow to the right hepatic artery. This patient had a right-sided iCCA with multiple lesions. The left hepatic artery was not transected to allow for a future right hemihepatectomy. The second patient had a branch from the aorta feeding the liver tumor that was recognized on preoperative imaging and underwent postoperative embolization rather than intraoperative ligation prior to undergoing the nuclear scan. The third patient had a dissection of the hepatic artery that was confirmed on postoperative angiography and could not be salvaged.

Postoperative nuclear imaging showed incomplete hepatic perfusion in 12 out of 148 patients (8.1%); three patients had delayed cross-perfusion after ligation of accessory and/or aberrant hepatic arteries, three patients had an early bifurcation of the proper hepatic artery, one patient (0.7%) had a missed accessory hepatic artery not ligated during surgery, 1 patient (0.7%) had a known adrenal artery feeding the liver tumor, and four patients had unexplained incomplete hepatic perfusion. None of these patients had a large tumor or ablation between the left and right liver that could have explained lack of cross perfusion. For all patients with incomplete hepatic perfusion on nuclear imaging, the postoperative note reported normal perfusion during intraoperative final methylene blue test.

Arterial complications and postoperative interventions

Postoperative digital subtraction angiography using the bolus channel of the pump identified an arterial complication in four

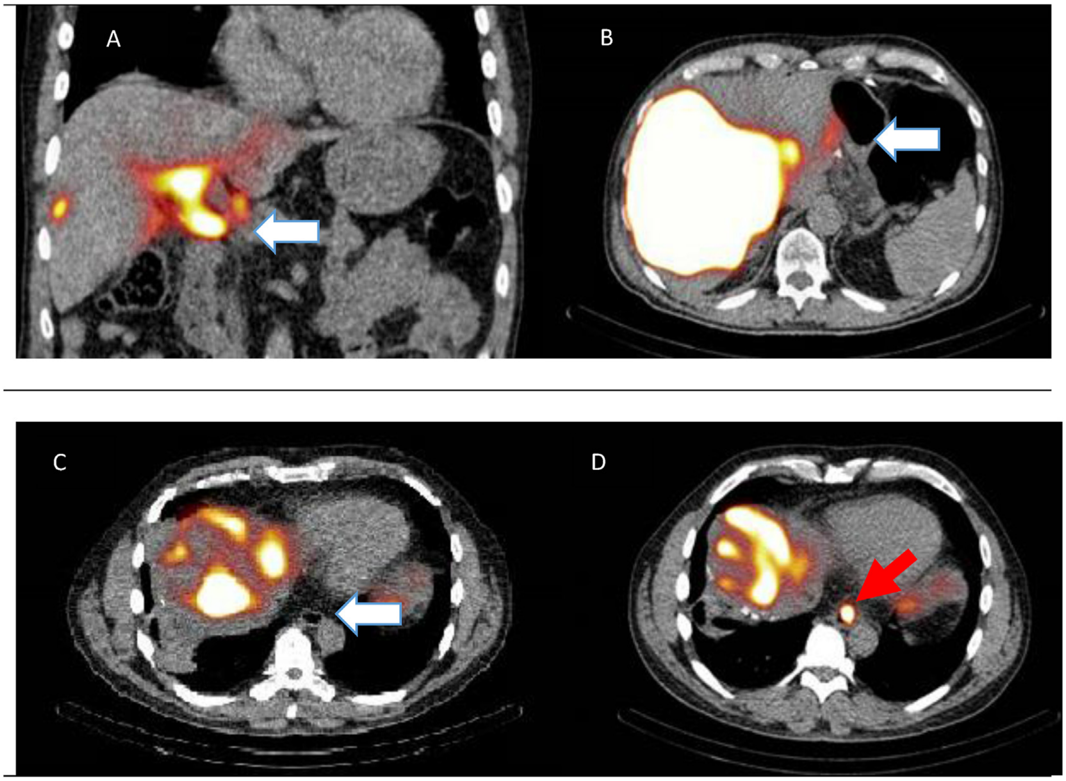

Figure 2 Abnormal findings on postoperative nuclear imaging. Two patients with extrahepatic perfusion detected in the wall of the common bile duct (A) and the stomach (B) on postoperative nuclear imaging (white arrows). Both were considered false positive findings; the former patient (A) underwent a venous phase CT showing physiological activity in the common bile. The latter underwent no further diagnostics (B). Both patients underwent uneventful HAIP floxuridine without requiring additional intervention. One patient developed a symptomatic distant esophageal ulcer after three cycles of HAIP floxuridine despite a normal postoperative nuclear imaging (C, white arrow). A repeat nuclear imaging confirmed extrahepatic perfusion (D, red arrow).

patients (2.7%). One patient had a thrombosis of the common hepatic artery, salvaged by postoperative endovascular stent placement. Three patients had a dissection of the hepatic artery; one was managed with endovascular stent placement, one was managed with anticoagulation, and one was unsalvageable. The patient with the unsalvageable dissection was the only patient (0.7%) who never received HAIP chemotherapy due to a pump or catheter-related complication. None of the 150 patients developed a pseudo-aneurysm or hemorrhage from the catheter insertion site after surgery or during follow-up.

Four patients (2.7%) underwent postoperative embolization (Table 3). In two patients, this was decided based on preoperative imaging before pump placement due to accessory arteries towards the tumor arising from the aorta or the adrenal artery. In two other patients, embolization was decided based on incomplete hepatic perfusion found on nuclear imaging. One patient had a small accessory right hepatic artery that was missed intraoperatively and not noticed on pre-operative imaging because no adequate arterial phase imaging was performed. The other patient had an early bifurcation of the proper hepatic artery with preferential flow to the right. Nuclear imaging after embolization of the left hepatic artery showed complete liver perfusion in both patients. Postoperative embolization was not performed in the other two patients with an early bifurcation of the proper hepatic artery with preferential right flow. The rationale was that sacrificing these arteries could interfere with future surgical treatment options for recurrence in the liver. No patients underwent postoperative embolization for extrahepatic perfusion. Postoperative nuclear imaging led to a change of management in only two patients (1.3%); one accessory hepatic artery missed on preoperative imaging and one patient with an early bifurcation of the proper hepatic artery with preferential right flow.

Clinical signs of extrahepatic perfusion during HAIP chemotherapy

One patient developed a floxuridine-induced ulcer in the distal esophagus after three HAIP floxuridine cycles, confirmed by gastroscopy and repeat nuclear imaging upon complaints of esophageal reflux and abdominal pain. No EHD was visible on the initial postoperative nuclear imaging (Fig. 2C). HAIP floxuridine treatment was discontinued and the patient recovered spontaneously within 6 weeks. No other patient developed

Table 3 Incomplete hepatic perfusion outcomes during intraoperative methylene blue testing and postoperative nuclear imaging

Outcome (n = 150)	n (%)	Postoperative embolization
Incomplete hepatic perfusion at final methylene blue test (n = 150)	***3 (2.0)***	***1***
Early bifurcation of the proper hepatic artery with preferential flow	1 (0.7)	None[a]
Known branch from the aorta to liver tumor	1 (0.7)	1[b]
Dissection of the hepatic artery, unsalvagable	1 (0.7)	None
Incomplete hepatic perfusion at nuclear imaging (n = 148)[c]	***12 (8.1)***	***3***
Explanation unknown	*4 (2.7)*	None
Early bifurcation of the proper hepatic artery with preferential flow	*3 (2.1)*	1
Delayed cross perfusion after ligated aberrant artery	*3 (2.1)*	None
Accessory right HA missed on preoperative imaging	*1 (0.7)*	1
Known adrenal artery to liver tumor	*1 (0.7)*	1[b]
Large tumor or ablation between left/right liver	*0*	–

All cases of incomplete hepatic perfusion detected through nuclear imaging were novel when compared with the methylene blue dye test.
[a] This patient had a right-sided unresectable iCCA. The left hepatic artery was left intact to allow for a future right hemihepatectomy.
[b] Less challenging to embolize postoperatively than dissect during surgery.
[c] Two patients did not undergo postoperative nuclear imaging; one patient had an unsalvageable hepatic artery dissection and did not undergo nuclear imaging, the other patient died before nuclear imaging was performed.

symptoms related to extrahepatic perfusion of floxuridine warranting nuclear imaging.

Discussion

Extrahepatic perfusion after HAIP placement was detected during intraoperative methylene blue testing in 29.3% of patients and was treated successfully in all patients by additional surgical dissection and ligation. The risk of clinically relevant extrahepatic perfusion on postoperative nuclear imaging was 0%. Incomplete hepatic perfusion was detected with nuclear imaging in 8.1% of patients. Only two patients (1.3%) underwent embolization for incomplete hepatic perfusion based on nuclear imaging; one patient with a missed accessory right hepatic artery and one patient with an early bifurcation of the proper hepatic artery with preferential flow to the right liver.

To our knowledge, this is the first prospective study describing the detection of extrahepatic perfusion and incomplete hepatic perfusion using both intraoperative methylene blue dye test and postoperative nuclear imaging prior to HAIP chemotherapy. A previous study reported an incidence of 2% of both extrahepatic perfusion and incomplete hepatic perfusion detected on postoperative nuclear imaging in 544 patients treated with upfront HAIP floxuridine between 1986 and 2001 in MSKCC for unresectable CRLM. All patients were able to start HAIP floxuridine and no HAIP floxuridine-related signs of gastroduodenal ulcers or pancreatitis were reported.[7] All patients with extrahepatic perfusion and 78% of incomplete hepatic perfusion were salvaged by postoperative embolization of additional arteries. The low incidence of extrahepatic perfusion and incomplete hepatic perfusion, as well as the high salvageability are consistent with the results of the current study.

Tablot et al. published a retrospective series of 233 patients who underwent surgical pump implantation for HAIP chemotherapy with floxuridine or 5-FU for various liver tumors between 1995 and 1998 in St George Hospital, Sydney. All patients underwent methylene blue testing during surgery but no postoperative nuclear imaging was performed.[6] Twenty patients (9%) presented with abdominal pain and had extrahepatic perfusion towards the duodenum and stomach, and seven (3%) patients had an ulcer, as diagnosed with endoscopy with methylene blue injection via the pump. All 20 patients developed symptoms of gastroduodenal ulceration within 6 months of HAIP implantation. However, no hospital readmissions were reported, suggesting mild morbidity. Additionally, the symptoms disappeared when treatment with HAIP chemotherapy was discontinued or additional arteries were embolized.

.Nuclear imaging to detect extrahepatic perfusion is also used prior to Selective Internal Radiation Treatment (SIRT) for unresectable liver tumors. In a study from 2015, 825 patients with unresectable liver tumors underwent injection of Technectium-99m-labeled human serum albumin into the hepatic arteries after transfemoral access; 54 patients (6.5%) showed extrahepatic perfusion.[24] The lower rate (i.e., 0%) of extrahepatic perfusion on nuclear imaging in the current study and other HAIP chemotherapy studies can be attributed to skeletonization of the hepatic arteries during surgery and methylene blue testing and ligation of extrahepatic vessels during surgery. Several small series have reported intra-arterial chemotherapy with a percutaneous approach.[25–27] The increased rate of extrahepatic perfusion was one of the drawbacks of this approach, in addition to hepatic artery thrombosis and infection due to the prolonged presence of a percutaneous catheter in the flow of the hepatic artery. However, lower complication rates may be seen with technical improvements, making this a minimally invasive approach with great potential.

Intraoperative methylene blue testing in this study had a high rate (29.3%) of detecting extrahepatic perfusion. Surgeons differ in the extent of dissection in the hepatoduodenal ligament for pump placement. Extensive dissection results in a ligament with only a bare portal vein, hepatic artery, and extrahepatic bile duct. The advantage is the low risk of extrahepatic perfusion during methylene blue testing. The disadvantage is the risk of intraoperative injury to these structures and theoretically a higher rate of bile duct ischemia. Less extensive dissection may be a better approach, followed by intraoperative methylene blue testing and additional dissection as needed. A commonly used alternative to methylene blue is indocyanine green, which is particularly suitable for a robotic platform.[28]

In the present study, not a single patient with clinically relevant extrahepatic perfusion was found using nuclear imaging. A zero-event rate, however, does not rule out positive findings for extrahepatic perfusion on nuclear imaging in future patients. The present study included only 150 patients and the upper limit of the 95% confidence interval for the risk of extrahepatic perfusion was 2.5%. Moreover, two patients (1.3%) with incomplete hepatic perfusion on nuclear imaging underwent embolization; one with an accessory right hepatic artery missed on inadequate preoperative imaging and one with an early bifurcation of the proper hepatic artery and preferential flow to the right. The missed accessory hepatic artery, however, could have been avoided with an adequate arterial phase CT scan. Moreover, an early bifurcation of the proper hepatic artery with potential preferential flow to the right is detected during preoperative arterial phase CT scan and during surgery. Routine postoperative nuclear imaging may therefore be needed only in patients with inadequate preoperative imaging, limited visualization during surgery, an unresolved abnormal intraoperative methylene blue test, or an early bifurcation of the proper hepatic artery to rule out preferential unilateral flow. In addition, nuclear imaging should be considered in any patient with abdominal complaints that could be attributed to extrahepatic exposure of floxuridine (e.g. gastroduodenal ulcers, pancreatitis). A selective use of postoperative nuclear imaging could result in large reduction in costs for patients receiving HAIP chemotherapy.

One patient (0.7%) developed a mild HAIP chemotherapy-induced gastroesophageal ulcer that was confirmed with repeat nuclear imaging, despite a normal methylene blue test and initial postoperative nuclear imaging; this may be due to delayed collateral formation after operative ligation of extrahepatic branches of the hepatic arteries. Although this risk is very small, the medical team should have a low threshold for nuclear imaging when symptoms develop during HAIP chemotherapy.

Six patients (4%) with unresolved incomplete hepatic perfusion underwent HAIP floxuridine (Table 3). Two patients had unilateral preferential flow due to an early bifurcation of the proper hepatic artery without embolization, three patients had delayed cross perfusion after ligation of aberrant or accessory hepatic arteries, and in the other four patients no explanation was found. The incidence of incomplete hepatic perfusion on postoperative nuclear imaging was too small to investigate the consequences. No published studies were found that have assessed the clinical consequences of incomplete hepatic perfusion. Incomplete hepatic perfusion may lead to disease progression in the liver segments that were not perfused with floxuridine, while potentially increasing toxicity in the overexposed segments of the liver. The consequences of administering HAIP floxuridine in patients with unresolved incomplete hepatic perfusion should be investigated in future research, in particular the pattern of unilateral disease progression and unilateral toxicity.

A strength of the present study is that all patients were part of multicenter clinical trials with safety as one of the outcomes. Consequently, surgical methylene blue test and nuclear imaging outcomes, and potential signs of extrahepatic perfusion during HAIP floxuridine treatment were monitored closely. Moreover, this study included all consecutive patients in the Netherlands, starting with the first patient treated with HAIP chemotherapy. This study also has some limitations. First, the outcome of the methylene blue test to detect extrahepatic perfusion and incomplete hepatic perfusion during surgery was collected retrospectively using operative notes. Incomplete hepatic perfusion identified on nuclear imaging was mostly not reported for the intraoperative methylene blue test. Identifying extrahepatic perfusion was the primary goal of the methylene blue test. Therefore, incomplete hepatic perfusion during intraoperative methylene blue testing was most likely not adequately perceived or recorded in the operative note. Secondly, although we found not a single patient with extrahepatic perfusion at nuclear imaging in 150 patients, we cannot rule out that in the next 150 patients we will detect patients with extrahepatic perfusion. In fact, the upper limit of the 95% confidence interval for the risk of extrahepatic perfusion was 2.5%. Finally, the incidence of extrahepatic perfusion with the methylene test was high and the test might have positive findings that may not be clinically relevant.

In conclusion, intraoperative methylene blue testing during pump placement for intra-arterial chemotherapy identified extrahepatic perfusion in 29.3% of patients, but could be resolved intraoperatively in all patients. Postoperative nuclear imaging found no clinically relevant extrahepatic perfusion and led to embolization in only 1.3% of patients. Complications of extrahepatic perfusion, however, can be severe. Therefore, the role of routine nuclear imaging after HAIP implantation should be studied in a larger cohort.

Data availability

The data used in this paper can be made available upon reasonable request.

Funding source

Erasmus MC Efficiency (Mrace), Erasmus MC Foundation, Coolsingel Foundation, Tricumed GmbH (in kind), The Dutch Cancer Society ("KWF Kankerfonds").

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Kemeny NE, Chou JF, Boucher TM, Capanu M, DeMatteo RP, Jarnagin WR *et al*. (2016) Updated long-term survival for patients with metastatic colorectal cancer treated with liver resection followed by hepatic arterial infusion and systemic chemotherapy. *J Surg Oncol* 113:477–484.
2. Thiels CA, D'Angelica MI. (2020) Hepatic artery infusion pumps. *J Surg Oncol* 122:70–77.
3. Ensminger WD, Rosowsky A, Raso V, Levin DC, Glode M, Come S *et al*. (1978) A clinical-pharmacological evaluation of hepatic arterial infusions of 5-fluoro-2'-deoxyuridine and 5-fluorouracil. *Cancer Res* 38(11 Pt 1): 3784–3792.
4. Ensminger WD, Gyves JW. (1983) Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 10:176–182.
5. Groot Koerkamp B, Sadot E, Kemeny NE, Gönen M, Leal JN, Allen PJ *et al*. (2017) Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: a propensity score analysis. *J Clin Oncol* 35:1938–1944.
6. Talbot ML, Clark JR, Clingan PC, Morris DL. (2002) Gastroduodenal ulceration following hepatic arterial chemotherapy: the role of methylene blue endoscopy in the investigation of pain. *HPB* 4:29–34.
7. Allen PJ, Nissan A, Picon AI, Kemeny N, Dudrick P, Ben-Porat L *et al*. (2005) 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* 201:57–65.
8. Daly JM, Kemeny N, Oderman P, Botet J. (1984) Long-term hepatic arterial infusion chemotherapy. Anatomic considerations, operative technique, and treatment morbidity. *Arch Surg* 119:936–941.
9. Doria MI, Jr., Doria LK, Faintuch J, Levin B. (1994) Gastric mucosal injury after hepatic arterial infusion chemotherapy with floxuridine. A clinical and pathologic study. *Cancer* 73:2042–2047.
10. Perez DR, Kemeny NE, Brown KT, Gewirtz AN, Paty PB, Jarnagin WR *et al*. (2014) Angiographic identification of extrahepatic perfusion after hepatic arterial pump placement: implications for surgical prevention. *HPB* 16:744–748.
11. Allen PJ, Stojadinovic A, Ben-Porat L, Gonen M, Kooby D, Blumgart L *et al*. (2002) The management of variant arterial anatomy during hepatic arterial infusion pump placement. *Ann Surg Oncol* 9:875–880.
12. Kemeny MM. (2001) The surgical aspects of the totally implantable hepatic artery infusion pump. *Arch Surg* 136:348–352.
13. Platform ICTR. (2022) *Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases in patients with a low clinical risk score - a feasibility study*. EU Clinical Trials Register. updated. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2016-004299-24-NL.
14. Buisman FE, Grunhagen DJ, Homs MYV, Grootscholten C, Filipe WF, Kemeny NE *et al*. (2019) 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* 26:4599–4607.
15. Platform ICTR. (2022) *Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases in patients with a low clinical risk score - a randomized controlled trial*. EU Clinical Trials Register. updated. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2018-001696-21-NL.
16. Buisman FE, Homs MYV, Grünhagen DJ, Filipe WF, Bennink RJ, Besselink MGH *et al*. (2019) Adjuvant hepatic arterial infusion pump chemotherapy and resection versus resection alone in patients with low-risk resectable colorectal liver metastases - the multicenter randomized controlled PUMP trial. *BMC Cancer* 19:327.
17. Platform ICTR. (2022) *Hepatic arterial infusion pump chemotherapy in patients with unresectable intrahepatic cholangiocarcinoma: trialsearch.who.in*. updated. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2018-004013-41-NL.
18. Platform ICTR. (2022) *Adjuvant hepatic arterial infusion pump chemotherapy after repeat hepatectomy for patients with liver confined recurrence of colorectal cancer – a phase II study: trialsearch.who.in*. updated. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=NL9294.
19. Platform ICTR. (2022) *Hepatic arterial infusion PUMP chemotherapy combined with systemIc chemoTherapy for potentially resectable colorectal liver metastases. The PUMP-IT study - the PUMP-IT pilot study: trialsearch.who.in*. updated. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019-003260-44-NL.
20. Lafon PC, Reed K, Rosenthal D. (1985) Acute cholecystitis associated with hepatic arterial infusion of floxuridine. *Am J Surg* 150:687–689.
21. Buisman FE, Filipe WF, Galjart B, Grünhagen DJ, Homs MYV, Moelker A *et al*. (2022 Mar) Adjuvant intra-arterial chemotherapy for patients with resected colorectal liver metastases: a systematic review and meta-analysis. *HPB* 24(3):299–308.
22. Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF *et al*. (1999) Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 341:2039–2048.
23. Wilson EB. (1927) Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 22:209–212.
24. Theysohn JM, Ruhlmann M, Müller S, Dechene A, Best J, Haubold J *et al*. (2015) Radioembolization with Y-90 glass microspheres: do we really need SPECT-CT to identify extrahepatic shunts? *PLoS One* 10e0137587.
25. Goéré D, Pignon JP, Gelli M, Elias D, Benhaim L, Deschamps F *et al*. (2018) Postoperative hepatic arterial chemotherapy in high-risk patients as adjuvant treatment after resection of colorectal liver metastases - a randomized phase II/III trial - PACHA-01 (NCT02494973). *BMC Cancer* 18:787.
26. Goéré D, Benhaim L, Bonnet S, Malka D, Faron M, Elias D *et al*. (2013) Adjuvant chemotherapy after resection of colorectal liver metastases in patients at high risk of hepatic recurrence: a comparative study between hepatic arterial infusion of oxaliplatin and modern systemic chemotherapy. *Ann Surg* 257:114–120.
27. Deschamps F, Rao P, Teriitehau C, Hakime A, Malka D, Boige V *et al*. (2010) Percutaneous femoral implantation of an arterial port catheter for intraarterial chemotherapy: feasibility and predictive factors of long-term functionality. *J Vasc Intervent Radiol* 21:1681–1688.
28. Galema HA, Meijer RPJ, Lauwerends LJ, Verhoef C, Burggraaf J, Vahrmeijer AL *et al*. (2022) Fluorescence-guided surgery in colorectal cancer; A review on clinical results and future perspectives. *Eur J Surg Oncol* 48:810–821.