Adjuvant hepatic arterial infusion pump chemotherapy after repeat hepatectomy for patients with liver confined recurrence of colorectal cancer – a phase II study

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

5-FU	**5-fluorouracil**
ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
ANC	**Absolute Neutrophil Count**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CEA	**Carcinoembryonic Antigen**
CHA	**Common Hepatic Artery**
CRLM	**Colorectal Liver Metastases**
CRC	**Colorectal Carcinoma**
CTCAE	**Common Terminology Criteria for Adverse Events**
CV	**Curriculum Vitae**
DHBA	**Dutch HepatoBiliary Audit**
DPYD	**Dihydropyrimidine Dehydrogenase**
DFS	**Disease Free Survival**
DSMB	**Data Safety Monitoring Board**
ECOG	**Eastern Cooperative Oncology Group**
EU	**European Union**
EHD	**Extrahepatic disease**
EudraCT	**European drug regulatory affairs Clinical Trials**
FUDR	**Floxuridine/ fluorodeoxyuridine**
GCP	**Good Clinical Practice**
GDA	**Gastroduodenal Artery**
GDPR	**General Data Protection Regulation**
GFR	**Glomerular Filtration Rate**
HAIP	**Hepatic Arterial Infusion Pump**
hDFS	**Hepatic Disease Free Survival**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IRE	**Irreversible Electroporation**
IMP	**Investigational Medicinal Product**

IMPD	**Investigational Medicinal Product Dossier**
MAA	**Macroaggragated Albumin**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MRI	**Magnetic Resonance Imaging**
MSKCC	**Memorial Sloan Kettering Cancer Center**
MWA	**Microwave Ablation**
OS	**Overall Survival**
PET	**Positron Emission Tomography**
PVE	**Portal Vein Ablation**
RCT	**Randomized Controlled Trial**
RFA	**Radiofrequency Ablation**
RV	**Reference Value**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Uitvoeringswet 'Algemene Verordening Gegevensbescherming**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Colorectal cancer (CRC) is the third most common cancer in the Netherlands. About 50% of patients develop colorectal liver metastasis (CRLM) throughout the course of the disease. Resection and/or ablation of the CRLM is the only curative treatment. Unfortunately, approximately 70% of patients develop recurrence, half of which is still confined within the liver. (1) Repeat hepatectomy has emerged as a viable therapy for recurrent CRLM showing comparable survival and morbidity as resection for index CRLM. (2-6) Consequently, the number of patients undergoing repeat resections for recurrent CRLM is increasing over the years. (7) This patient group has withstood the test of time for developing extrahepatic recurrences. Currently, no effective adjuvant treatment options are available for this patient population. Even after repeat hepatectomy for recurrent CRLM, half of the recurrences after resection of recurrent CRLM occur in the liver. (3-5, 7) Therefore optimal disease control within the liver may lead to improved disease-free survival and overall survival.

Treatment with hepatic arterial infusion pump (HAIP) chemotherapy allows high dosage chemotherapy to be directed into the liver without the chemotherapy reaching other organs. The drug used, floxuridine (a 5-FU analogue), has a 95% first pass effect in the liver. (8) In addition CRLM derive most of their blood supply from the hepatic artery, rather than the portal vein. (9, 10) By administering high dose floxuridine in the liver, microscopic liver metastasis that are invisible during imaging are also tackled, thus preventing growth of these micrometastases at a later stage.

Floxuridine is best delivered with a subcutaneous pump that can deliver high dose floxuridine continuously for two weeks and is accessible through the skin.

Hepatic arterial infusion pump chemotherapy has been developed and evaluated in Memorial Sloan Kettering Cancer Center (MSKCC) and has been implemented in standard guidelines for treatment for metastatic colorectal cancer confined to the liver. In a recent retrospective study of 2378 patients treated in MSKCC, patients receiving adjuvant HAIP chemotherapy after resection of index CRLM had an Overall survival (OS) benefit of 2 years compared with those that did not receive HAIP chemotherapy. (11) Preliminary results of a retrospective study including 363 patients treated in MSKCC and the Erasmus MC show that patients that have received adjuvant HAIP chemotherapy after repeat hepatectomy for CRLM had an hepatic disease frees survival (hDFS) of 50 months compared with 18 months in patients that received resection only (p=0.003). This translated to an overall survival (OS) of 89 and 57 months with and without adjuvant HAIP chemotherapy respectively (p=0.01).(12) Due to the retrospective

nature of the studies, the results could be subjected to bias. However, such promising results deserve further research with a prospective study design.

Objective: The primary objective is to evaluate the efficacy of repeat hepatectomy and adjuvant HAIP chemotherapy in patients with recurrent resectable colorectal liver metastases. Secondary objectives are DSF, OS, postoperative complications and adverse events during the treatment course

Study design: A multi center phase II study.

Study population: Adults with resectable recurrent CRLM without evidence extrahepatic disease (EHD) throughout the course of the disease.

Intervention: HAIP chemotherapy with floxuridine will be administered in 6 cycles.

Main study parameters/endpoints: The primary endpoint is hepatic disease free survival (hDFS). Secondary endpoints include OS, disease free survival (DFS) and postoperative complications, adverse events.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The intervention comes in addition to the standard of care. A pump will be surgically implanted at the time of curative-intent liver resection. Prior to the first administration of HAIP chemotherapy a technetium-99-labeled macroaggregated albumin nuclear medicine scan is performed to confirm bilobar hepatic perfusion and rule out extrahepatic perfusion. Patients will proceed with 6 cycles of chemotherapy. Follow-up after treatment is identical to the standard of care.
Surgical complications related to HAIP pump placement are uncommon (<10%), but include hepatic artery thrombosis, pump pocket infection, and arterial haemorrhage at the site of arterial catheter insertion. The radiation dose of the Tch99 MAA scan is 3-4 mSv. A total of 5-10 ml contrast agent will be infused which with a negligible effect on renal function. HAIP chemotherapy will require two hospital visits for each cycle, with a maximum total of 12 visits. HAIP chemotherapy toxicities include ulcer disease and biliary sclerosis, which can both be largely avoided by imaging prior to treatment and monitoring of liver tests and dosages adjustments, if needed. Systemic side effects with HAIP chemotherapy of floxuridine are rare (<1%).

The expected benefit in median hDFS found in preliminary research with more than 300 patients was 32 months in favour of adjuvant HAIP chemotherapy versus resection alone (50 months versus 18 months respectively).

1. INTRODUCTION AND RATIONALE

Background

Colorectal liver metastasis

Colorectal cancer (CRC) is the third most common cancer in the Netherlands. About 50% of patients develop colorectal liver metastasis (CRLM) throughout the course of the disease. Resection and/or ablation of the CRLM is the only curative treatment. Unfortunately, approximately 70% of patients develop recurrence, half of which is still confined within the liver. (1) Repeat hepatectomy has emerged as a viable therapy for recurrent CRLM showing comparable survival and morbidity as resection for index CRLM. (2-6) Moreover, currently around 14% of patients undergoing liver resection have a medical history of previous liver directed surgery. (13) Consequently, the number of patients undergoing repeat resections for recurrent CRLM is increasing over the years.(7) This patient group has withstood the test of time for developing extrahepatic recurrences. At present, no effective adjuvant treatment options are available for this patient population. Even after repeat hepatectomy for recurrent CRLM, half of the recurrences after resection of recurrent CRLM occur in the liver. (3-5, 7) Therefore optimal disease control within the liver may lead to improved disease-free survival and overall survival.

Hepatic arterial infusion pump chemotherapy

Mechanism of action

Hepatic arterial infusion pump (HAIP) chemotherapy for liver tumors is a treatment that has been developed at Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA). It is currently not available in the European Union, because floxuridine is not registered in the EU. The biological rationale for intra-arterial chemotherapy is that the hepatic artery rather than the portal vein is responsible for most of the blood supply to liver tumors.(9, 10) Moreover, up to 95% of drugs such as floxuridine (FUDR) is extracted by the liver during the first-pass, allowing an up to 400-fold increase in hepatic exposure with minimal systemic exposure.(8, 14) Intra-arterial chemotherapy is delivered in the hepatic artery via a surgically implantable pump with a catheter in the gastroduodenal artery. The pump is filled percutaneously and the liver is continuously perfused with the infusion solution for two weeks, which is repeated after a two-week rest period.

Treatment with hepatic arterial infusion pump (HAIP) chemotherapy allows high dosage chemotherapy to be directed into the liver without the chemotherapy reaching other organs. The drug used, floxuridine (a 5-FU analogue), has a 95% first pass effect in the liver. (8) In addition CRLM derive most of their blood supply from the hepatic artery, rather than the portal

vein. (9, 10) By administering high dose floxuridine in the liver, microscopic liver metastasis that are invisible during imaging are also tackled, thus preventing growth of these micrometastases at a later stage.

Floxuridine is best delivered with a subcutaneous pump that can deliver high dose floxuridine continuously for two weeks and is accessible through the skin.

In a recent retrospective study of 2368 patients treated in MSKCC, patients receiving adjuvant HAIP chemotherapy after resection of index CRLM had an Overall Survival (OS) benefit of 2 years compared with those that did not receive HAIP chemotherapy. (11) Preliminary results of a retrospective study including 323 patients treated in MSKCC and the Erasmus MC show that patients that have received adjuvant HAIP chemotherapy after resection of recurrent CRLM had an hepatic disease free survival (hDFS) of 50 months compared with 18 months in patients that received resection only (p=0.003). This translated to an overall survival (OS) of 89 and 57 months with and without adjuvant HAIP chemotherapy respectively (p=0.01). Due to the retrospective nature of the studies, the results could be subjected to bias. However, such promising results deserve further research with a prospective study design.

Safety and feasibility

HAIP chemotherapy is a complex treatment with a large involved multidisciplinary team. Both subcutaneous placement of the pump and the administration of HAIP chemotherapy itself are complex procedures. Adverse events have been well characterized in the setting of MSKCC.(15) A pilot study evaluating adjuvant HAIP chemotherapy in patients with index CRLM in Erasmus MC and Antoni van Leeuwenhoek (AvL) concluded that the treatment is feasible and can be safely provided in the Netherlands.(16). “Safe” means that adverse events of both surgical placement of the pump and administration of HAIP chemotherapy are justifiable compared with the expected survival benefit. “Feasible” means that our multidisciplinary team can administer HAIP chemotherapy to the majority of eligible patients. Currently the Erasmus MC is running a multicenter randomized controlled trial (RCT) to evaluate the efficacy of adjuvant HAIP chemotherapy vs resection alone in patients with resectable CRLM (NTR7493).

Imaging to assess adequate perfusion of pump

Prior to the first administration of intra-arterial chemotherapy, bilobar hepatic perfusion and lack of extrahepatic perfusion are confirmed by post-operative technetium-99-labeled macroaggregated albumin (MAA) nuclear medicine scanning. MAA is administered through the IP2000V bolus port. Within 1 hour after MAA injection, a SPECT/CT scan is performed.

The total radiation dose of the Tch99 MAA scan is approximately 3-4 mSv. This has been the default method of imaging in MSKCC.

2. OBJECTIVES

Primary Objective:

The first objective of this study is to evaluate efficacy of adjuvant HAIP chemotherapy after repeat hepatectomy for recurrent CRLM in the Erasmus MC as measured by hDFS.

Secondary Objective(s):

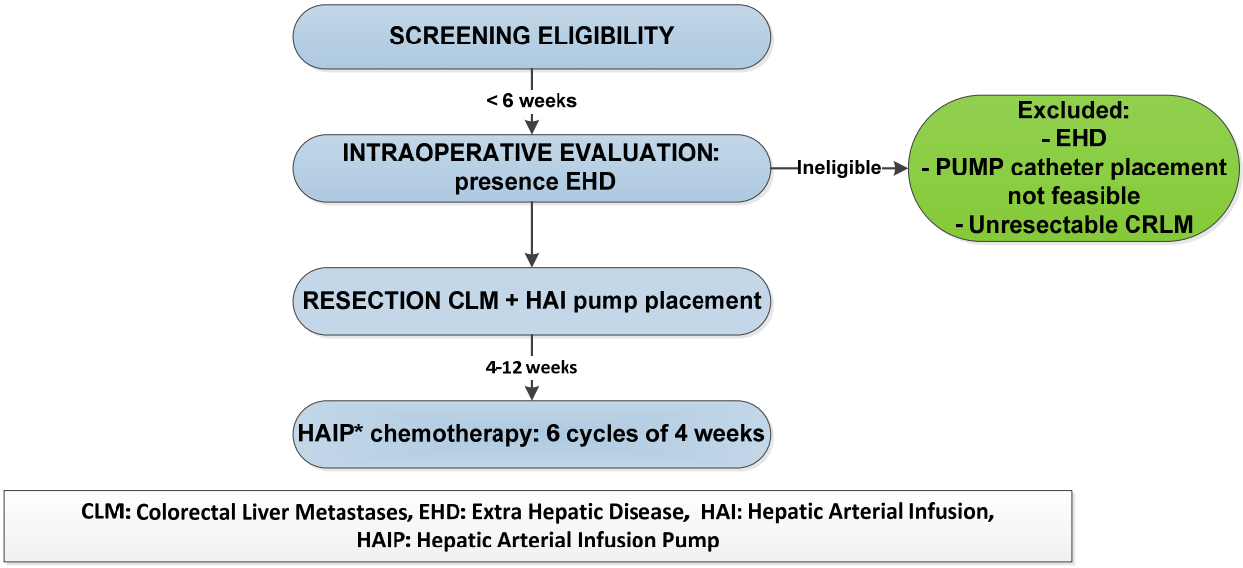
Secondary objectives are DFS, OS, postoperative complications and adverse events during the treatment course.

3. STUDY DESIGN

This is a prospective study to determine the efficacy of adjuvant HAIP chemotherapy for hepatic only recurrence of CRLM after previous resection of CRLM in the Netherlands.

The study design is presented in the figure below. The expected inclusion period is 3 years. Follow-up for the primary outcome is one year after inclusion of the last patient. The total study duration is therefore 4 years. Follow-up will continue after the study to capture long-term survival outcomes.

Study design: Adjuvant HAIP chemotherapy after resection of CRLM



The principal investigator is the primary surgical oncologist performing the HAIP implantations in patients participating in the PUMP pilot and PUMP RCT studies (NTR6917, NTR7493 respectively) (16, 17). Furthermore, he is currently involved in proctoring HAIP implantation in other centers in the Netherlands. At the time of writing this protocol more than 50 patiënts have successfully undergone HAIP implantations. All patients that have received the HAIP have successfully started with their first HAIP chemotherapy cycle. Dr. N. Kemeny, medical oncologist at MSKCC and pioneer of HAIP chemotherapy, has shared her detailed protocols with our medical oncologists. The research team in the Netherlands was trained by medical oncologists (Dr. N. Kemeny and Dr. A. Cercek), surgical oncologists (Dr. M.I. D'Angelica, Dr. T.P. Kingham, and Dr. R. DeMatteo), and nurse practitioners from MSKCC during a two-day workshop. The participating centers all have ample experience with the intervention due to participation in the ongoing PUMP –I trial for index CRLM (NTR7493). Additionally, the team at MSKCC will be available 24-7 for proctoring and advice where needed.

4. STUDY POPULATION

4.1 Population (base)

Adults with recurrent resectable CRLM without a history of EHD.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years.
- ECOG performance status 0 or 1.
- Histologically confirmed colorectal cancer (CRC).
- Liver only recurrence after previous local treatment of index CRLM
- Radiologically confirmed and resectable CRLM. Criteria for resectability are outlined in section 5.1.
- Positioning of a catheter for HAIP chemotherapy is technically feasible (see chapter 5) based on a CT with excellent arterial phase. The default site for the catheter insertion is the gastroduodenal artery (GDA). Accessory or aberrant hepatic arteries are no contraindication for catheter placement. The GDA should have at least one branch to the liver remnant; accessory or aberrant hepatic arteries should be ligated to allow for cross perfusion to the entire liver through intrahepatic shunts.
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 15 days prior to inclusion:
    - Absolute neutrophil count (ANC) ≥1.5 x 109/L
    - Platelets ≥100 x 109/L
    - HB ≥ 5.5 mmol/L
    - Total bilirubin ≤ 1.5 UNL
    - ASAT ≤ 5 x UNL
    - ALAT ≤ 5 x UNL
    - Alkaline phosphatase ≤ 5 x UNL
    - (Calculated) glomerular filtration rate (GFR) >30 ml/min.
- Written informed consent must be given according to ICH/GCP, and national/local regulations.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- A positive history of extrahepatic disease (including positive portal lymph nodes) at any time since CRC diagnosis. Patients with small (≤ 1 cm) extrahepatic lesions that are too small to characterize are eligible.
- Second primary malignancy except in situ carcinoma of the cervix, adequately treated non-melanoma skin cancer, or other malignancy treated at least 5 years previously without evidence of recurrence.
- CRLM requiring two-staged liver resections
- Recurrence CRLM at same location as previously unsuccessfully (i.e. residual disease) resected/ablated CRLM and <6 months after its resection.
- Known DPYD-deficiency.
- Pregnant or lactating women.
- History of psychiatric disability judged by the investigator to be clinically significant, precluding informed consent or interfering with compliance for HAIP chemotherapy.
- Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator.
- Organ allografts requiring immunosuppressive therapy.
- Serious, non-healing wound, ulcer, or bone fracture.
- Chronic treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisolone equivalent excluding inhaled steroids).
- Serious infections (uncontrolled or requiring treatment).
- Inclusion in another interventional clinical study with survival as primary outcome.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

4.4 **Sample size calculation**

According to our preliminary results a hDFS of 50 months with HAIP chemotherapy compared with 18 months without HAIP chemotherapy should be employed in the sample size calculation (12). However, considering possible overestimation in hDFS survival benefit with HAIP chemotherapy in the setting of retrospective data, we decided to select a sample size large enough to demonstrate a doubling in hDFS from 18 to 36 months with HAIP chemotherapy.

DFS will be estimated using the Kaplan-Meier method. For the sample size calculation, we used the One Arm Nonparametric Survival tool developed by Cancer Research And

Biostatistics (https://stattools.crab.org/Calculators/oneNonParametricSurvivalColored.htm; accessed May 24,2019).

In order to reject H0: median hDFS ≤ 18 months, assuming a median DFS ≥ 36 months, two-sided significance level $\alpha = 0.05$, power $1 - \beta = 0.8$, a 3-year inclusion period and one year additional follow-up, a total number of 39 patients are needed. To overcome possible dropout, 45 patients will be registered in the trial.

The median DFS along with a 95% confidence interval will be calculated using the Kaplan-Meier method. The null hypothesis will be rejected if the Kaplan-Meier estimate of the median DFS is 36.34 months or higher.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

General eligibility

Patients with histologically confirmed primary CRC, have previously undergone resection for index CRLM and have radiologically confirmed resectable liver only recurrence. Minimum requirement for the diagnosis of CRLM and the exclusion of EHD is a 3-phase CT scan of the chest, abdomen, and pelvis. If the CT-scan is older than 6 weeks at inclusion a new scan should be performed. MRI scanning of the liver is optional to further characterize indeterminate lesions. A PET-scan is optional to exclude EHD. Patient history, physical exam, and laboratory test to address all inclusion and exclusion criteria should be performed prior to inclusion.

Operability

All patients are screened by their treating physician for performance status to undergo liver surgery. In case of doubt, clearance by an anaesthesiologist is mandatory prior to inclusion. The patient should be operable to be eligible.

Resectability

A panel of local experts should assess resectability based on liver imaging. Resectability is defined as the opportunity to achieve complete resection with an adequate liver remnant. The liver remnant should comprise a portal vein, a hepatic artery, a bile duct, and one of the three main hepatic veins. The liver remnant should consist of at least 2 segments free of tumor with adequate liver function.

If liver volume or function is expected to be inadequate after resection, the following procedures are permitted to make the tumor resectable:

- Tumor ablation with radiofrequency ablation (RFA), microwave ablation (MWA), or irreversible electroporation (IRE) in combination with liver resection if the number of lesions to be treated with RFA does not exceed 3 and the largest diameter of ablated lesions is below 3 cm.
- Preoperative portal vein embolization (PVE) may be used to increase the liver volume of the future remnant liver.

Operation: complete resection of CRLM

Anaesthesia

The patient undergoes anaesthesia according to local hospital procedures.

Abdominal exploration

The abdomen is explored to rule out EHD. Suspected EHD should be confirmed by intra-operative biopsy with frozen section or cytology. Portal and celiac lymph nodes that are macroscopically suspicious to contain metastases are potential sites of EHD and should be evaluated by intra-operative biopsy with frozen section. An intra-operative ultrasound evaluation of the liver is recommended to assure the feasibility of complete resection of the CRLM with an adequate liver remnant. If so, the patient is eligible for HAI pump placement (section 5.1.1). If at exploration the surgeon finds unresectable disease or liver anatomy unfeasible for pump catheter placement, the pump placement is cancelled. These patients are excluded from analysis.

Tumor resection and ablation

Surgical resection of CRLM may include wedge resections, segmentectomies, or (extended) hemihepatectomy depending of the number, size, and site of CRLM. Vascular inflow control prior to parenchymal transection is optional. Parenchymal resection may be conducted by all standard techniques. Tumor ablation is allowed under conditions as described above.

Postoperative procedures

According to local hospital procedures.

Pathology specimen

According to local hospital procedures. An R0 resection is defined as the absence of tumor cells at the resection margin (i.e. margin >0mm).

Time frames and duration of therapy

Patients included in the study should have their surgery within 6 weeks after signing the informed consent.

Concomitant therapy

Other systemic anti-cancer therapy for the CRLM is prohibited while patients are on study therapy. The use of NSAIDs is discouraged during HAIP treatment. In case of concomitant use of acenocoumarol, the metabolism of acenocoumarol can be decreased when combined with

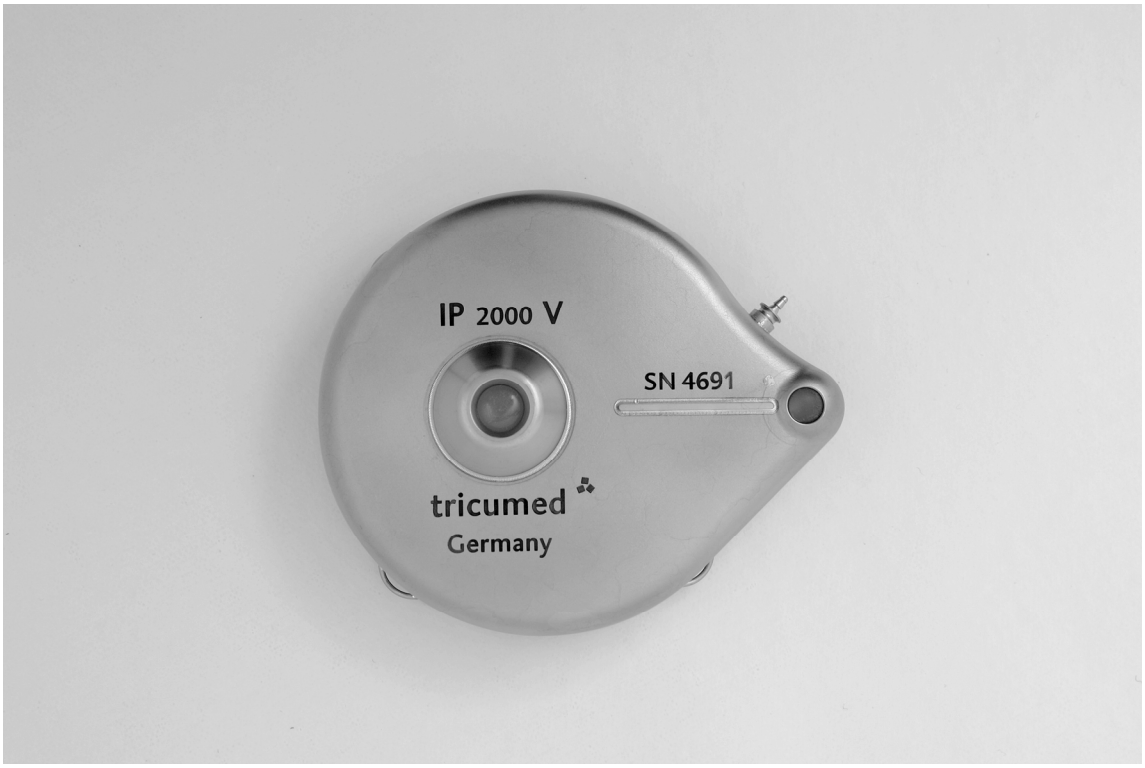
floxuridine. Close monitoring of INR or *switch to LMWH (at the discretion of the treating medical oncologist) is warranted*.

Pump implantation

Operation – HAI pump placement

After resection of the CRLM, all patients will receive an implantable infusion pump (Tricumed IP2000V Infusion Pump, 35ml, CE number: I7120728744042), pump catheter, intra-arterial catheter and a connector to connect the two catheters. This implantation will be used to administer HAIP chemotherapy. The pump is compatible with the use of intravascular infusion of floxuridine. The Spinal Catheter Set 4000 (CE number: 81001-1052010) contains a catheter and a catheter connector; the catheter will be connected with the infusion pump, while the connector will be used to connect the pump catheter to the intra-arterial catheter of B.Braun, (CE: 04430042). This intra-arterial catheter has beads that allow for securing the catheter with non-absorbable ties in the gastroduodenal artery (GDA). At the time of writing the protocol, Tricumed is developing an alternative PUMP catheter which. This catheter has a distal beaded design for intra-arterial use (identical to the abovementioned catheter of B.Braun). Once this catheter is CE marked it will be able to replace the Spinal Catheter set 4000 and intra-arterial catheter of B.Braun.

Figure A. The Tricumed IP2000V pump



Site of HAIP catheter placement

The catheter is positioned in the GDA allowing perfusion of the entire liver without obstructing the flow in the hepatic artery. In patients with abnormal hepatic arterial anatomy, the GDA is still the preferred site, as long as it connects with a proper hepatic artery perfusing at least one segment of the liver. Perfusion of the entire liver can be achieved in these patients by ligating all accessory and replaced hepatic arteries. Intrahepatic shunts will typically reassure that the catheter perfuses all liver segments, which can be confirmed with a bolus injection of methylene blue in the pump after clamping accessory and replaced hepatic arteries.

If the GDA is not suitable for catheter placement because of small calibre (rare) or absence of the GDA, the bifurcation of the proper hepatic artery into a left and right hepatic artery can be used. After an (extended) hemihepatectomy, the stump of the artery of the resected liver can be used as a conduit for the catheter. In minor liver resections, the left hepatic artery can be sacrificed for retrograde placement of the catheter with perfusion of the right hepatic artery, resulting in cross-perfusion of the entire liver through intrahepatic shunts. Cross-perfusion can sometimes not be confirmed intraoperatively. However, most patients will eventually develop cross-perfusion after four weeks, as will be ascertained with a postoperative nuclear scan.

Technique HAIP catheter and pump placement

The common hepatic artery (CHA) and the GDA are both palpable superior to the body of the pancreas and the first portion of the duodenum. The GDA runs parallel to and lies immediately to the left of the common bile duct, and it is advisable to start by dissecting the CHA to minimize the risk of injuring the bile duct. The right gastric artery is ligated and divided. The distal CHA, the entire GDA, and the proximal proper hepatic artery are dissected circumferentially from their attachments. The full length of the extrapancreatic GDA is mobilized over 2-3 cm to facilitate insertion of the catheter. Suprapyloric side branches of the GDA are often encountered and must be ligated. Frequently, branches to the pancreas and duodenum arise from many of these dissected vessels, and it is essential to identify and ligate these branches to avoid inadvertent perfusion of the pancreas, stomach, or duodenum. The common hepatic artery is mobilized 1 cm proximally, and the proper hepatic artery is mobilized about 2 cm distally from the origin of the GDA. Branches to the retroperitoneum from the right or left hepatic artery are common and should be ligated. Review of preoperative CT angiography to look specifically for these branches is important, because they are often found in retrospect. At this point, a complete circumferential dissection of the common hepatic artery, GDA, and proper hepatic artery should be ensured such that no vessels to the pancreas, stomach, or duodenum remain. The GDA should be temporarily occluded with palpation of the proper hepatic artery to rule out retrograde flow to the liver through the GDA secondary to celiac artery stenosis.

The pump pocket should be created in the left lower abdomen so that the pump lies below the waist and avoids contact with the iliac spine and the edge of the ribs. (Figure B) In obese patients, placing the pump over the ribs should be considered, because this may help in locating and accessing the pump. The pump and catheter should be handled carefully, avoiding contact with the patient's skin. The catheter is tunneled through the abdominal wall into the abdominal cavity. The pump is secured to the abdominal fascia with nonabsorbable sutures; the catheter should be positioned behind the pump to prevent injury by a needle. The catheter that comes attached to the pump is then connected with the intra-arterial catheter that has rings close to the tip to facilitate fixating the catheter to the artery with ties.

The GDA is then ligated with a nonabsorbable tie as far away from the CHA as possible, and vascular control of the common and proper hepatic arteries is achieved with vascular clamps or vessel loops. Isolated vascular control of the GDA at its orifice also can be used to avoid occlusion of the hepatic artery. An arteriotomy is made in the distal GDA, and the catheter is inserted up to, but not beyond, the junction with the hepatic artery. If the catheter protrudes into the common hepatic artery, turbulence of blood flow can lead to thrombosis of the vessel. Failure to pass the catheter to the junction leaves a short segment of the GDA exposed to full concentrations of floxuridine without the diluting effect of blood flow, potentially resulting in sclerosis, thrombosis, or late dislodgment. When positioned, the catheter should be secured with three nonabsorbable ties proximal to the tying rings on the catheter. Perfusion of both lobes of the liver and lack of extrahepatic perfusion is confirmed by a bolus injection of 2 to 3 mL of methylene blue. After the perfusion test, the catheter is flushed with heparinized saline, and the wounds are closed.

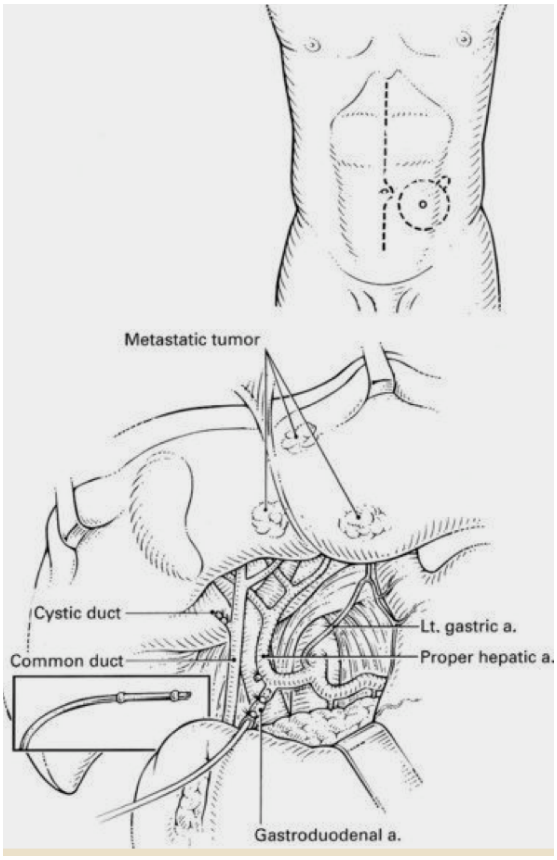


Figure B. Placement of the catheter in the gastroduodenal artery (GDA), Right gastric artery is shown adjacent to the GDA and is ligated.

Postoperative procedures

Prior to the first administration of intra-arterial chemotherapy, bilobar hepatic perfusion and lack of extrahepatic perfusion are confirmed by post-operative technetium-99-labeled macroaggregated albumin (MAA) nuclear medicine scanning. MAA is administered through the IP2000V bolus port. Within 1 hour after MAA injection, a SPECT/CT scan is performed.

The scans are obtained after recovery from surgery, just prior to hospital discharge. Patients with extrahepatic perfusion are evaluated angiographically and aberrant branches embolized with re-testing prior to treatment. All other postoperative procedures are done according to local hospital procedures.

Pathology specimen

According to local hospital procedures.

Time frames and duration of therapy

Patients will receive HAIP chemotherapy in cycles of 4 weeks, see section 5.1.2 for the detailed drug treatment plan. If patients fail to finish the complete regimen, they will stay on study.

Quality control procedures

The HAIP pump placements will be supervised by surgeons of MSKCC. Medical oncologists and oncology nurses will be trained by MSKCC staff for management of patients on HAIP chemotherapy. MSKCC staff will always be available to discuss HAIP chemotherapy management.

5.1.1 Drug Treatment Plan

HAIP chemotherapy after resection of CRLM

All patients start HAIP chemotherapy 4 to 12 weeks after surgery, after confirmation of perfusion of the whole liver and lack of extrahepatic perfusion.

Co-medication

See below.

HAIP chemotherapy: Drug Information floxuridine.

The drug that is used for HAIP is fluorodeoxyuridine or floxuridine (FUDR, Hikma Pharmaceuticals USA Inc.). Floxuridine has been administered using HAI pumps since the early 80s for patients with (recurrent) CRLM in the adjuvant, neo-adjuvant, and induction chemotherapy setting.(15, 18-26) Floxuridine has a half-life of 10 minutes and the liver extracts 95% of floxuridine during the first pass.(8) Toxic effects have been well characterized and are described in detail below. The most important serious adverse drug reaction is biliary toxicity. Floxuridine is commercially available. Further details are described in the Summary of Product Characteristics. (Appendix A)

Drug Administration

The pump reservoir is filled percutaneously with 0.12 mg/kg floxuridine together with 35,000 U of heparin, 25 mg of dexamethasone, and enough normal saline for a total volume of 35cc. For patients who are more than 25% above ideal body weight, the actual dose of floxuridine is calculated by using a weight that averages the patient's actual weight and their ideal weight.

Patients will have HAIP administered in a 4 weeks cycle. On day 1, the pump reservoir is filled. On day 15, the pump is emptied and refilled with heparinized saline (35,000 IU of heparin and enough normal saline for a total volume of 35 cc) for 2 weeks. Until completion of HAIP

chemotherapy, patients will receive prophylactic omeprazole 20mg once daily. The use of NSAIDs is discouraged during HAIP treatment.

Premedication

No premedication is administered.

Patient Monitoring

No standard patient monitoring is required after filling of the HAI pump.

Dose Adjustments

Patients' complete blood counts and liver function tests are monitored every 2 weeks during HAIP chemotherapy. In the case of abnormal blood tests, dose reduction or postponement of HAIP chemotherapy is done according to the protocol (Table 1) that has been used at MSKCC for many years.

Table 1. Dose Adjustment

	Reference Value (RV)* Upper limit of normal	% FUDR dose
Aspartate aminotransferase	2-3 * RV	80%
	3-4 * RV	50%
	>4 * RV	Hold
Alkaline phosphatase**	1.2-1.5 * RV	50%
	>1.5 * RV	Hold
Total bilirubin**/***	1.2-1.5 * RV	50%
	>1.5 * RV	Hold

*Reference value is defined as the patient's value on the first day of the most recent floxuridine cycle. The current value is defined as the highest recorded value since the reference value, i.e. the highest value on day 14 of the most recent floxuridine dose and day 1 of the current cycle.

**If patient's Alkaline Phosphatase or total bilirubin shows a continual rise from Day 1 of treatment, then the Day 1 value will be used as the reference value for that patient when determining whether to hold treatment, and time of re-treatment after hold.

*** Bilirubin elevation without any other elevation elevations in Alkaline Phosphatase or ASAT may be due to dehydration and reductions should not be followed in this case.

Dose reductions are per permanent, no dose escalations are allowed after dose reductions.

If treatment is held for any of the above situations, treatment will not be reinstituted until values

come down below 3* RV for aspartate aminotransferase or below 1.2*RV for alkaline phosphatase or total bilirubin, at which time treatment will resume at 25% of the last dose received. In case of treatment held the pump should be emptied and dexamethasone 25mg plus 35,000 IU of heparin and enough normal saline to fill the pump reservoir should be placed in the pump for 14 days. Additionally, a daily dose of 600mg ursodiol will be started in case of treatment stop due to bilirubin elevation. A skipped cycle should not be caught up later on.

If the patient develops a total bilirubin level above 51 mmol/L (i.e. 3.0 mg/dL), the pump should be emptied and dexamethasone 25mg plus 35,000 U of heparin and enough normal saline to fill the reservoir with 35cc. Once there is no longer evidence of toxicity, the dexamethasone dose should be tapered in increments of maximum 5mg every 14 days. Tapering will continue unless enzymes increase. Floxuridine should be permanently discontinued. Epigastric pain unresponsive to H2 blocker use should prompt a diagnostic workup including a technetium scan to rule out extrahepatic perfusion and an upper endoscopy to assess ulcer disease.

Duration of Therapy

Patients will receive HAIP chemotherapy with floxuridine for 6 cycles of 4 weeks. After the end of adjuvant treatment the removal of the subcutaneous pump will be discussed with both the patient and the local expert panel. If the pump is removed, the catheter is tied off and will be left in place at the fascial level. Alternatively, the pump can be left in place for possible HAIP chemotherapy at the time of hepatic recurrence.

5.1.2 Expected toxicities

Expected toxicities of HAIP chemotherapy of floxuridine

Systemic side effects with HAIP of floxuridine almost never occur; in particular, myelosuppression, nausea, and vomiting do not occur.(27) Diarrhoea is rare and should raise the suspicion of shunting of floxuridine to the bowel. Ulcer disease and biliary sclerosis are the most common toxicities. Ulcer disease results from inadvertent floxuridine perfusion of the stomach and duodenum that can be avoided by ligating all branches from the hepatic artery to the stomach and duodenum. Ulcer disease should be suspected when a patient develops severe epigastric pain after administration of the first dose. Diagnosis is confirmed with upper endoscopy and treated with embolization of the hepatic artery branch responsible for extrahepatic perfusion. If an ulcer or gastroduodenitis will be identified, therapy will be withheld for one month to allow healing. Pain treatment and proton-pump inhibitors will be started therapeutically. Severe abdominal pain or diarrhoea during hepatic arterial infusion will require

immediate emptying of the drugs from the pump and the instillation of heparin-treated saline until the result of the workup will be available.

The bile ducts are particularly sensitive to HAIP chemotherapy because they derive most of their blood supply from the hepatic artery. Close monitoring of liver enzymes and dose adjustment (as described in section 5.1) are necessary to avoid biliary sclerosis. Patients with severe biliary sclerosis may sometimes require percutaneous or endoscopic drainage and stent placement. A CT scan should be performed prior to biliary drainage to rule out intrahepatic recurrence causing biliary obstruction.

Expected complications related to the HAI pump

Surgical complications related to HAI pump placement may occur. A retrospective review of 544 HAI pump placements was performed at MSKCC.(15) Pump placement was typically combined with a partial liver resection. A simultaneous partial colectomy was performed in 136 patients (25%). No mortality attributed to the pump was reported. The most common complications were unrelated to the pump: wound infection of the laparotomy wound, atelectasis, prolonged ileus, and intra-abdominal abscess. Pump related morbidity (including dysfunction) occurred in 120 patients (22%). HAIP chemotherapy with floxuridine was impossible or discontinued in only 9% of patients. In 9 patients (2%) extrahepatic perfusion was found postoperatively, which could be resolved in 7 patients. In 9 patients (2%) postoperative technetium scan showed incomplete liver perfusion. Most common explanation was a non-ligated accessory or replaced hepatic artery, which was resolved with embolization or surgical ligation. Cross-over flow developed instantly or could be confirmed after four weeks. Hepatic arterial thrombosis can occur immediately after surgery (13 patients, 2%), of which a third could be salvaged with anti-coagulation. Thrombosis also occurred in 11 patients (2%) as a late complication resulting from HAIP chemotherapy. Pump pocket infection was found in 24 patients (4%) and could be salvaged with parenteral antibiotics in half of these patients. Simultaneous partial colectomy did not increase the rate of pump pocket infection. Arterial haemorrhage occurred in only 1 patient. The incidence of biliary sclerosis due to HAIP chemotherapy in a retrospective analysis of 293 patients was 5.5%. Risk factors most significantly associated with biliary sclerosis were dose, number of cycles, abnormal nuclear medicine scan, and postoperative infections. All patients were managed successfully with biliary stenting and/or dilatation.(28)

5.2 Use of co-medication

At study initiation, patients should report their concomitant medications to the physician.

5.3 Escape medication

Supportive care for treatment-related symptoms will be offered as needed to all patients in this study.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Patients will receive 6 cycles of floxuridine (FUDR). See section 5.1 for the description of investigational products.

6.2 Summary of findings from non-clinical studies

These are summarized in the Summary of Product Characteristics, see appendix A.

6.3 Summary of findings from clinical studies

These are summarized in the Summary of Product Characteristics, see appendix A.

6.4 Summary of known and potential risks and benefits

These are summarized in the Summary of Product Characteristics, see appendix A. For a structured risk analysis see section 13.

6.5 Description and justification of route of administration and dosage

See section 5.1 for the description and justification of route of administration and dose.

6.6 Dosages, dosage modifications and method of administration

See section 5.1 for the description and justification of route of administration and dose.

6.7 Preparation and labelling of Investigational Medicinal Product

According to local standard.

6.8 Drug accountability

According to local standard.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable, as this is not a study with a non-investigational product.

7.1 Name and description of non-investigational product(s)

Not applicable, as this is not a study with a non-investigational product.

7.2 Summary of findings from non-clinical studies

Not applicable, as this is not a study with a non-investigational product.

7.3 Summary of findings from clinical studies

Not applicable, as this is not a study with a non-investigational product.

7.4 Summary of known and potential risks and benefits

Not applicable, as this is not a study with a non-investigational product.

7.5 Description and justification of route of administration and dosage

Not applicable, as this is not a study with a non-investigational product.

7.6 Dosages, dosage modifications and method of administration

Not applicable, as this is not a study with a non-investigational product.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable, as this is not a study with a non-investigational product.

7.8 Drug accountability

Not applicable, as this is not a study with a non-investigational product.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary aims is to determine the efficacy, determined by hDFS, of resection and adjuvant HAIP chemotherapy in patients with liver only recurrence after previous resection of CRLM. hDFS is defined as the time between surgery and the first event defined as recurrence in the liver or death, or last follow-up, whichever comes first.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcome are OS, DFS, postoperative Clavien-Dindo grade III or higher complications until 90 days after surgery and HAIP chemotherapy related adverse events of grade III or higher (CTCAE grade III or higher; appendix B) until the the last refill of the infusion pump. OS is defined as the time between surgery and the first event defined as death. DFS is defined as the time between surgery and the first event defined as recurrence of disease at any site or death.

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomization, blinding and treatment allocation

Not applicable, as this is not a randomized or blinded study.

8.3 Study procedures

Before start treatment

- Full eligibility check as described in section 4.
- Written informed consent
- Medical history including medication assessment
- Physical examination (incl. height, weight, and vital signs)
- ECOG-performance status

Laboratory assessments

- Carcinoembryonic Antigen (CEA)
- Haematology and blood chemistry: Hemoglobin, ANC, platelets, total bilirubin, ASAT, ALAT, gamma-GT, AF, GFR, Na, K, APTT/INR
- Serum pregnancy test (for all women less than 2 years amenorrhoeic)

Imaging and diagnostic studies

- CT scanning of the abdomen and chest with 3-phase scanning of the liver, including an excellent arterial phase.
- Definitive diagnosis of CRLM is made by CT scanning; no biopsy of the CRLM is required.

Before administration of HAIP chemotherapy, during admission

Imaging

Technetium-99-labeled macroaggregated albumin nuclear medicine scan.

During treatment

Treatment related serious adverse events (SAE) and adverse events (AE) of grade III or higher (chemotherapy related according CTCAE 5.0) will be collected continuously from the time of study inclusion until 4 weeks after the end of treatment. AE are followed up until the event is either resolved or adequately explained, even after the patient has completed his/her study treatment. Patient history, vital signs, weight, ECOG Performance Status, Toxicity assessment (AE grade III or higher), haematology, and liver function tests will be assessed at each visit during HAIP chemotherapy. Nature and duration of any hospitalization, treatment of any AE, and nature and duration of any outpatient care will be recorded. Any SAE's related to the pump will be recorded to the manufacturer.

After the end of treatment (i.e. follow-up)

Evaluation of efficacy

Efficacy is evaluated with the primary outcome hDFS after resection and adjuvant treatment with HAIP chemotherapy.

Hepatic Disease Free Survival

hDFS is defined as the time between surgery and the first event defined as recurrence in the liver or death, or last follow-up, whichever comes first.

Overall Survival

OS is defined as the time between surgery and the first event defined as death.

Disease Free Survival

DFS is defined as the time between surgery and the first event defined as recurrence of disease at any site or death. Recurrence is evaluated with imaging modalities (typically CT

scan) at pre-specified intervals. A rise in serum tumor marker (e.g. CEA) is insufficient to establish recurrence. In case of doubt, a histologic biopsy can provide definitive proof of progression. DFS is measured from the date of surgery to the date of progression, death, or last follow-up.

Evaluation of complications

Toxicity

Toxicity will be graded from the time of study inclusion up to the day of the last refill procedure of the infusion pump and is recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Postoperative complications

Surgical complications will be defined according to the standard classification of surgical complications (Table 2). Only complications of Clavien-Dindo grade 3 or higher are recorded for the first 90 days after surgery. (29) Postoperative complications include those related to the HAI pump placement. Postoperative mortality is defined as any death during hospitalization or within 90 days from surgery.

Table 2. Classification of surgical complications

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anaesthesia
Grade IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic

attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Follow- up

Follow-up will be performed according the standard care in the Netherlands. Postoperative complications will be reported until 90-days after surgery (Clavien-Dindo classification, grade III or higher). Next, treatment related adverse events grade III or higher (chemotherapy related according CTCAE, grade III or higher) will be reported until 4 weeks after the end of treatment. Follow-up visits may coincide with visits for HAIP chemotherapy treatment.

Follow-up starts from the day of operation.

First follow-up moment: 2-4 weeks after surgery

First and second year: every 3 months (starting from date operation)

Third to fifth year: at least every 6 months until the end of follow-up 5 years after surgery.
The first visit after operation will be primarily for discussion of the pathology result of the resected specimen(s). Surgical complications will be recorded (see above).
Assessment for recurrence (abdominal and pelvic CT including 3-phase liver imaging and chest CT) will be done according to the current guidelines, i.e. at least once every 6 months after surgery until the end of follow-up after 5 years or until a confirmed recurrence. Follow-up imaging will also be done at the discretion of the treating physician if the patient shows signs of a recurrence (e.g., clinical status deteriorating or a rising CEA). Possible re-operation and/or further cancer therapy will be recorded.

Assessments at follow-up visits

- Every visit: ECOG performance status
- Every visit: CEA (not at first visit)
- At least once every 6 months: CT of the abdomen, chest, and pelvis, including 3-phase CT of the liver (not at first visit)

Table 3. Evaluation summary table.

	Prior to study inclusion	After surgery during admission	1st visit (2-4 weeks after surgery)	Every 2 weeks during HAIP chemotherapy	After surgery, in months.													
					3	6	9	12	15	18	21	24	30	36	42	48	54	60
Written informed consent	X																	
Eligibility check	X																	
Operability check	X																	
Resectability check	X																	
Medical history[1]	X																	
CEA	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and blood chemistry[2]	X		X	X														
Pregnancy test[3]	X																	
CT scan chest and abdomen[4]	X[5]				(X)	X	(X)	X	(X)	X	(X)	X	X	X	X	X	X	X
Nuclear scan		X																
ECOG performance status	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Surgical complication score			X		X													
Chemotherapy toxicity score			X	X	X	X	X											
Vital signs (incl weight)	X		X	X														

[1)] Medical history; ASA classification, severe cardiac comorbidity y/n, severe pulmonary comorbidity y/n, exclusion criteria.
[2)] Hematology and blood chemistry: Hemoglobin, ANC, platelets, total bilirubin, ASAT, ALAT, gamma-GT, AF, GFR, Na, K.
[3)] If applicable.
[4)] Follow-up CT scans will be performed every 3-6 months postoperatively during the first 2 years after surgery and every 6 months thereafter until the end of follow-up at 60 months postoperatively.
[5)] MRI scanning of the liver is optional to further characterize indeterminate lesions. A PET-scan is optional to exclude extrahepatic disease.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Specific criteria for withdrawal are:

- Non-compliance of the patient
- Refusal to continue protocol treatment

8.5 Replacement of individual subjects after withdrawal

An excluded patient will be replaced in if patient does not meet the inclusion criteria between the time of inclusion and before start of protocol treatment (i.e. complete resection not feasible or indicated). Patients that have started the protocol treatment (i.e. start of pump implantation procedure) will not be replaced. The goal of replacing excluded patients is preservation of sample size.

8.6 Follow-up of subjects withdrawn from treatment

Patients who are withdrawn from treatment will be followed as described in the schedule of assessments for follow up. For patients who are withdrawn from treatment because in hindsight they did not fulfill the eligibility criteria at time of enrolment, data will be collected until 30 days after the last protocol treatment given. SAE information will be collected as described in 9.2.2. No further information will be collected for patients who have withdrawn their consent. Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

8.7 Premature termination of the study

The Sponsor may decide to terminate the study prematurely based on the following criteria:

- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved.

The Sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of the decision to terminate the study. The Sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. Adverse events (grade 3 of higher) reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation (i.e. at least a 24h period) or prolongation of existing inpatients' hospitalisation; excluding planned or elective hospitalization
- results in persistent or significant disability or incapacity;
- required intervention to prevent permanent impairment or damage
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Progression of the disease under study is not considered an SAE.

The local investigator will decide whether or not the SAE is related to study treatment. The decision will be recorded on the serious adverse event report. The assessment of causality is made by the local investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
RELATED	There is evidence to suggest a causal relationship

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

If SAE's (due to either surgical or chemotherapeutic treatment) occur from the day of surgery, these should be reported to the sponsor at least up to 30 days after treatment.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will be responsible for SUSAR assessment and will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

The study coordinator will ensure reporting of any SUSARS to the Ethics Committee (EC), the competent authority (CA), and the investigators in the Erasmus MC.

9.3 **Annual safety report**

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 **Follow-up of adverse events**

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 **Data Safety Monitoring Board (DSMB)**

Data and Safety Monitoring Board will not be installed. Monitoring of data and safety will be performed as described in the monitoring plan (see chapter 12.2: Monitoring and Quality Assurance). A DMSB is installed in the currently open PUMP trial, in which the same intervention is assessed in patients with resectable index CRLM (NTR7493).

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The median hDFS along with a 95% confidence interval will be calculated using the Kaplan-Meier method. The null hypothesis will be rejected if the Kaplan-Meier estimate of the median hDFS is 36.34 months or higher.

10.2 Secondary study parameters/endpoints

The median OS and DFS along with a 95% confidence interval will also be calculated using the Kaplan- Meier method. Other secondary outcome are adverse events grade III or higher (chemotherapy related according CTCAE version 5.0, grade III or higher, appendix B) until 4 weeks after the end of treatment. The proportion and 95% confidence interval will be calculated.

10.3 Other study parameters

Not applicable

10.4 Interim analysis

Interim analyses will not be performed for survival outcomes. Interim analyses are performed for postoperative complications (grade 3 or higher) and AE (SAE plus AE of grade 3 or higher) for early detection of unusually high rates of complications and AE. Interim analyses are planned after including 20 patients.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (64th World medical Association General Assembly, Fortaleza, Brazil, October 2013) or the laws and regulations of the country, whichever provides the greatest protection of the patient. In particular the Dutch laws and regulations with the WMO. ("Wet Medisch-wetenschappelijk Onderzoek met mensen").

11.2 Recruitment and consent

Written informed consent of patients is required before enrolment in the study and before any study related procedures take place.

The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. This includes explaining the study to the patient, providing him/her with information such as the expected efficacy and possible side effects, and that refusal to participate will not influence further options for therapy. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient. There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the study is scheduled to close for enrolment.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable as no minors or incapacited subjects are enrolled in this study.

11.4 Benefits and risks assessment, group relatedness

Based on preliminary results assessing the survival benefit of adjuvant which are currently under review for publication, a hDFS of 50 months (95% CI 13-86 months) was found in patients treated with adjuvant HAIP chemotherapy compared to 18 months (95%CI 13-23 months) in patients treated with resection only (HR 0.59, 95% CI 0.42-0.84, p=0.003). This translated to an OS of 89 months (95% CI 52-126 months) and 57 months (95%CI 47-67 months) in patients treated with and without adjuvant HAIP chemotherapy respectively (HR 0.61, 95% CI 0.42-0.90, p=0.01).

Based on these preliminary results we concluded that HAIP chemotherapy may provide a substantial survival benefit for patients with recurrent CRLM.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 650.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;

2. € 5.000.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who cpate in the Research;

3. € 7.500.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Patient confidentiality

Research data will be stored in a Castor EDC database (or any comparable data capture system that meets the Erasmus MC requirements) and will be handled confidentially. Research data that can be traced to individual persons can only be viewed by authorized personnel. These persons are the members of the research team, members of the health care inspection, and members of the Medical Research Ehtics Committee of the participatin hospital. Data review may be necessary in order to ensure the reliability and quality if the research. The handling of personal data is in compliance with the EU General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet 'Algemene Verordening Gegevensbescherming' (UAVG)).

Each patient is assigned a unique patient study number (e.g. A-01 or B-03) at enrolment. In study documents the patient's identity is coded by patient study number as assigned at enrolment.

The investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and can only be accessed by the investigator and the supporting site staff, and by representatives of the Sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

Case Report Forms

Data will be collected on electronic Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data to be collected on the e-CRF are derived from the protocol.

Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the Sponsor's auditor and inspection by the regulatory authority(ies).

The investigator should file all essential documents relevant to the conduct of the study on site in the Investigator Site File. The Sponsor will file all essential documents relevant to the overall conduct of the trial in the Trial Master File. Essential documents should be filed in

such a manner that they are protected from accidental loss and can be easily retrieved for review.

Record retention

Essential documents should be retained for 20 years after the end of the study (i.e. from date of last patient visit for this study). They should be destroyed after this time.
Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the study. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

12.2 Monitoring and Quality Assurance

The study will be monitored in accordance with the study specific monitoring plan compliant with NFU guidelines and the Erasmus MC requirements. The monitor will evaluate at least the safety, which is also the primary outcome parameters at regular intervals, in compliance with the 'minimal' risk class assessment A.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority (CCMO).

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject,

numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority (CCMO).

12.6 Public disclosure and publication policy

Publications resulting from this study will be submitted to peer-reviewed journals. The principle investigators and study coordinators will prepare the manuscript together with those who substantially contributed to the study. Specification for authorship have been summarized in the appendix (appendix C). Any publication, abstract or preservation based on patients included in this study must be approved by the primary investigators and the study coordinators. This is applicable to any individual patient registered in the trial, or any subgroup of the trial patients.

13. STRUCURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Floxuridine is a 5-FU derivative and one of the oldest known chemotherapeutics. Intra-arterial delivery in the hepatic artery at a very high dose is tolerated because of the 95-99% first-pass effect with minimal systemic side effects.(8, 25)

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

HAIP chemotherapy with floxuridine (FUDR) has been extensively investigated in MSKCC in New York and other centers, including several phase 2 trials and a phase 3 trial.(23, 24, 30-35)

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Both have been performed and proven successful.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

e. Analysis of potential effect

Biliary sclerosis is the most important side effect, arising because the bile ducts receive most of their blood supply from the hepatic artery. Biliary sclerosis is closely monitored with lab values immediately before and after HAIP chemotherapy. Dose adjustments are pre-specified based on extensive experience at MSKCC. (28, 36) All other complications of HAIP chemotherapy are outlined in appendix B.

f. Pharmacokinetic considerations

The half-life of floxuridine (FUDR) is only 10 minutes. Continuous high levels in the tumor are realized because liver tumors receive most of their blood supply from the hepatic artery (rather than the portal vein) and the pump delivers floxuridine continuously in the hepatic artery for two weeks each cycle.

g. Study population

Patients with resectable colorectal liver metastases, without extrahepatic disease.

h. Interaction with other products

In case of concomitant use of acenocoumarol, the metabolism of acenocoumarol can be decreased when combined with floxuridine. Close monitoring of INR is warranted. (www.drugbank.ca)

i. Predictability of effect

The majority of recurrences after repeat hepatectomy for CRLM occur in the liver. HAIP chemotherapy is a liver directed therapy that has been found to increase disease control in the liver, translating to an increased survival. Due to the small group of patients that have been treated with adjuvant HAIP chemotherapy after repeat hepatectomy for CRLM no subgroup analysis has been made to identify variables that may predict efficacy of adjuvant HAIP chemotherapy after repeat hepatectomy.

j. Can effects be managed?

Patients will be seen frequently at the outpatient clinic for control visits. Patients are also included in the regular care system of patients treated with anticancer therapy which means that they can contact, or can be seen 24h/day, in case of any problems.
No antidote of antagonist is available. Biliary sclerosis is the most important side effect and is closely monitored with lab values immediately before and after HAIP chemotherapy. Dose adjustments are pre-specified based on extensive experience at MSKCC. Endoscopic or percutaneous drainage and stenting is available but rarely required for progressive biliary sclerosis and biliary obstruction.

13.2 **Synthesis**

Surgical placement of the pump

The risks of pump placement have been described in detail in a study of more than 500 patients.(15) Severe surgical complications are rare and include hepatic arterial thrombosis (2%), catheter dislodgement (<0.1%), severe hemorrhage (<0.1%), and pump pocket infection (4%).

HAIP chemotherapy

The safety of HAIP chemotherapy with floxuridine has been extensively investigated in patients with CRLM. Side effects of HAIP chemotherapy are known from a study of 544 patients in which no death was attributed to HAIP chemotherapy.(15) Serious adverse events or adverse events of grade 3 or higher are rare and include biliary toxicity sometimes requiring biliary drainage and ulcer disease.(15, 28)

The Tricumed IP2000V pump was found to be compatible with the use of floxuridine.

Technetium-99-labeled macroaggregated albumin nuclear medicine scan

Widely used diagnostic test making unknown risks unlikely. The total radiation dose of the Tch99 MAA scan is only 3-4 mSv.

Measures to reduce risks

To minimize the risks for patients enrolled in this study, we have taken quality control measures for surgery. HAIP pump placement will be performed or supervised by surgeons who have reached the plateau of the learning curve.(15) This will include surgeons from MSKCC.

We use protocols developed at MSKCC to avoid or minimize side effects of HAIP chemotherapy. For example, a nuclear scan is performed to rule out extrahepatic perfusion that may cause ulcer disease. Other side effects such as biliary toxicity are minimized with extensive monitoring of lab values and a protocol for dose reductions.

We have a collaboration agreement with the team at MSKCC guaranteeing 24/7 support.

Unknown and overall risk assessment

Unknown risks are unlikely given that this treatment has been used in more than thousand patients in the USA. Moreover, a study reported detailed adverse events for more than 500 patients.(15) The main risks involve surgical placement of the pump and administration of HAIP chemotherapy. These risks have been described and quantified in detail. No death has been attributed to the pump.(15) Severe postoperative complications and serious adverse events may arise. However, the probability and severity are considered acceptable compared to the expected benefit up to 3 years in overall survival.(37) Based on the guideline by the NFU (Dutch Federation of University Medical Centers) about quality insurance in human research (“Kwaliteitsborging van mensgebonden onderzoek”) we qualify the risk of this study as ‘low’ (small chance of serious damage).(38)

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APPENDICES

14.1 Appendix A: Summary of Product Characteristics Floxuridine

The summary of the characteristics of floxuridine (FUDR) is available via the link displayed below.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c8edabc1-67cd-421b-a147-7c1f19f05b8e

14.2 **Appendix B: Common Terminology Criteria for Adverse Events**

In the present study, adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (November 27, 2017).

At the time this protocol was issued, the full CTC document was available at the following URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

14.3 **Appendix C: authorship of publications**

The final publication of the trial results will be written by the study coordinator on the basis of the final analysis. A draft manuscript will be submitted by the principle investigators and other co-authors. The manuscript will subsequently be sent to a scientific journal.

Authors of the manuscript will include at least the study coordinator, coordinating investigator, principle investigators and co-investigators (one oncologist and one liver surgeon per site). Authors must have contributed substantially to the study and must have had input in the manuscript.

All manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, as well as supporting bodies. The coordinating investigator must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered in the study, or any subgroup of the study patients.