Colorectal Liver Metastases

Intra-arterial Pump Chemotherapy

Florian E. Buisman

Copyright © F.E. Buisman, Rotterdam 2021

ISBN: 978-94-6423-470-1

This thesis was partly realized due to the financial support of Erasmus University Medical Center, Department of Surgery Erasmus MC, Disphar International,
Tricumed Medizintechnik GmbH, Van den Bogeart en Partners, Coloplast, Erbe Nederland, De Research Manager, Servier Nederland Farma, ABN AMRO, B. Braun, Raadsheeren, ChipSoft, and Blaak & Partners.

Research in this thesis was financially supported by KWF Dutch Cancer Society, Tricumed Medizintechnik GmbH (in kind), Stichting Coolsingel, Erasmus MC Mrace, Erasmus MC Fellowship, and unrestricted grants of Las Moras and Burando.

Colorectal Liver Metastases

Intra-arterial Pump Chemotherapy

Colorectale levermetastasen
Intra-arteriële chemotherapie via de chemopomp

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defense shall be held on
Tuesday 12 October 2021 at 13:00 hours

by

Florian Eduard Buisman
born in Schiedam, the Netherlands

Erasmus University Rotterdam

Promotiecommissie

Promotoren	Prof. dr. C. Verhoef
	Prof. dr. M.I. D'Angelica
	Dr. B. Groot Koerkamp
Overige leden	Prof. dr. S. Sleijfer
	Prof. dr. P.J. Tanis
	Prof. dr. H.M.W. Verheul
Copromotor	Dr. D.J. Grünhagen

Table of contents

Chapter 1

General introduction and
Outline of this thesis

General introduction

Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer worldwide, accounting for up to 1.8 million new patients in 2018.[1] In 2018, approximately 14.000 patients were diagnosed with CRC in the Netherlands.[2] The prognosis of CRC is highly associated with the stage of the disease. About 50% of patients with CRC can be cured with surgical resection with or without (neo)adjuvant treatment.[3, 4]

About 25% of patients have synchronous metastases at time of diagnosis of CRC. Approximately 50% of patients develop metastases during follow-up after curative-intent resection of CRC.[5] Frequent locations of metastatic disease are the liver, lung, lymph nodes, and the peritoneum.[6, 7] In most patients with metastases, cure is not possible. Palliative chemotherapy, however, does improve survival.

Colorectal liver metastases

Colorectal liver metastases (CRLM) are the most common metastases in patients with colon cancer. Synchronous CRLM and metachronous CRLM account for approximately 40% of all metastases in CRC patients.[8] CRLM are thought to originate from the venous drainage of the colon through the portal vein.[9] Curative-intent treatment of CRLM with complete resection or ablation is feasible in about 20% of these patients. At 10-years after resection of CRLM, about 20% of patients are alive without disease.[10]

The efficacy of resection of CRLM has never been evaluated in a randomized controlled trial (RCT). However, 10-year survival without resection of CRLM is exceedingly rare.[10-12] Resection (with/without ablation) is therefore the standard of care. Liver resections for CRLM have been performed since the second half of the 20th century. At that time, resection was limited to patients with one to three unilobar CRLM with a very high associated postoperative mortality. Over the past decades, the criteria for resection have been extended. Resectability is related to both anatomical and biological factors. The only anatomical requirement is now a complete resection with an adequate liver remnant. Morbidity and mortality of resection decreased as a result of improved surgical techniques (e.g., parenchyma sparing resection, two-staged resection, and intra-operative ultrasound) and improved perioperative care (e.g., preoperative portal vein embolization, and imaging).[11, 13, 14] Unfortunately, up to 70% of patients develop recurrences within the first two years after resection.[10]

About 80% of patients with CRLM have unresectable CRLM and/or extrahepatic disease. Prognosis is poor, and treatment is often limited to palliation and supportive care. The trade-off between possible life extension by palliative treatment (i.e., chemotherapy, radiation, and palliative surgery) and the risk of toxicities that affect the quality of life should be considered carefully. Fluoropyrimidines (e.g., 5-FU) with leucovorin (LV) demonstrated to prolong

survival in the palliative setting.[15] Several RCTs demonstrated superior response rates of regimes that include a combination of oxaliplatin/irinotecan and conventional 5-FU/LV (e.g., FOLFOX and FOLFIRI) compared to 5-FU/LV monotherapy in patients with advanced CRC.[16-19] Targeted therapies, such as monoclonal antibodies to vascular endothelial growth factor (e.g., bevacizumab) and to epidermal growth factor (e.g., cetuximab and panitumumab), showed improved response rates in selected patients in addition to the conventional chemotherapy in metastatic CRC patients.[20, 21] These treatments have also been investigated in patients with resectable CRLM.

Perioperative therapy for resectable CRLM

Perioperative systemic treatment aims to reduce the recurrence rate and consequently prolong survival after resection of CRLM. Three main entities are systemic chemotherapy, targeted therapy, and intra-arterial chemotherapy.

Systemic chemotherapy

The efficacy of perioperative systemic chemotherapy in patients with resectable CRLM is still debatable. Perioperative systemic chemotherapy was found to improve progression-free survival (PFS), but not overall survival (OS) in a large RCT after a median follow-up of 8.5 years.[22, 23] In this RCT, 364 patients were assigned to either 6 cycles of preoperative with 6 cycles of postoperative FOLFOX chemotherapy or resection alone. Long-term follow-up demonstrated a statistically significant improvement of PFS of perioperative FOLFOX in only the per-protocol analysis (21 months vs. 13 months, $p = 0.04$). No statistically significant difference in OS could be demonstrated (median OS 63 months vs. 55 months, $p = 0.30$). It appears that while systemic chemotherapy delays progression of disease, it does not obviously prolong OS. Another RCT randomized 306 patients to FOLFIRI or 5-FU alone.[24] No difference in 3-year PFS rate (25% vs. 22%, $p = 0.47$) or 3-year OS rate (73% vs. 72%, $p = 0.69$) was found.

In some countries (e.g., USA), perioperative systemic chemotherapy is the standard of care in patients with resectable CRLM; in other countries (e.g., the Netherlands) it is not. The guidelines for the management of patients with metastatic CRC of the European Society for Medical Oncology (ESMO) recommend upfront resection in patients with favorable prognostic criteria. However, in patients with unfavorable prognostic criteria (including synchronous CRLM) perioperative systemic chemotherapy is recommended. In patients that have not received preoperative chemotherapy for metastatic disease, adjuvant chemotherapy with CAPOX or FOLFOX is recommended, unless patients were recently treated with adjuvant oxaliplatin-based chemotherapy.[25] The United States National Comprehensive Cancer Network guidelines (NCCN) recommend perioperative systemic chemotherapy for a maximum period of 6 months in patients with resectable CRLM. The NCCN guidelines do not recommend which treatment sequence of resection and systemic chemotherapy (preoperative, adjuvant, or both) is preferred.[26]

Targeted therapies

Both the ESMO and NCCN guidelines do not support the use of additional targeted treatments in patients with upfront resectable CRLM. A phase III RCT (n = 77) found a similar disease-free survival (DFS) and OS of patients treated with adjuvant capecitabine with oxaliplatin (CAPOX) compared to CAPOX with additional bevacizumab, however this trial was closed prematurely due to slow accrual.[27] Another RCT (New EPOC study) found no PFS and OS benefit for cetuximab in addition to perioperative systemic chemotherapy (FOLFOX or CAPOX) in 236 KRAS wildtype patients with resectable CRLM.[28]

Intra-arterial chemotherapy

In specialized centers, intra-arterial chemotherapy has been utilized for selected patients in the past decades. A catheter is fixed in the hepatic artery which is attached to an internal pump that is positioned in the subcutaneous tissue of the left lower quadrant of the abdomen.[29] This allows delivery of continuous chemotherapy (i.e., hepatic arterial infusion pump (HAIP) chemotherapy). Alternatively, external pumps are used that usually require percutaneous catheter insertion.[30]

Intra-arterial chemotherapy can reduce the intrahepatic recurrence rate after curative-intent resection of CRLM. Several studies showed superior survival of HAIP chemotherapy after CRLM resection. The largest RCT using floxuridine, included 156 patients that were assigned to adjuvant HAIP chemotherapy with floxuridine and systemic 5-FU vs. adjuvant systemic 5-FU alone.[31, 32] HAIP chemotherapy demonstrated superior 2-year OS (86% vs. 72%, $p = 0.03$), and median PFS (31 months vs. 17 months, $p = 0.02$). Recently, a large propensity score analysis of 2368 patients, including 785 patients treated with HAIP, showed a survival benefit with HAIP chemotherapy of almost two years (67 vs. 43 months, $p < 0.001$).[33] This difference remained after adjusting for 7 prognostic factors: HR 0.67, 95% CI 0.59-0.76, $p < 0.001$). Patients with a low clinical risk score (89 vs. 53 months, $p < 0.001$) and node negative CRC seemed to benefit most (129 vs. 51 months, $p < 0.001$).

Prognostication and personalized treatment

Prognostic factors

Patient and disease related factors have been useful for prognostication. Usually multiple factors are combined to estimate survival probabilities. Existing prognostic models for CRLM provide information on recurrence or duration of survival after resection of CRLM. The clinical risk score (CRS) of Fong is the most simple and best known model and is the sum of five poor prognostic factors, assigning one point to each factor if present: positive nodal status of primary tumor, disease-free interval between resection of primary and diagnosis of CRLM less than 1 year, more than one CRLM, size of largest CRLM exceeds 5 cm, and preoperative serum carcinoembryonic antigen (CEA) level above 200 µg/L. Patients can be stratified into low-risk (0-2 points) and high-risk (3-5 points) of recurrence.[34]

Predictive factors

Predictive factors (i.e., KRAS status for cetuximab) estimate the effectiveness of treatment. For example, a previous study suggested that HAIP chemotherapy was more effective in patients with a low CRS (89 months vs. 53 months, $p < 0.001$) compared to patients with high CRS (50 months vs. 37 months, $p < 0.001$).[33] On the contrary, several retrospective studies found that perioperative systemic chemotherapy is in particular effective in patients with a high CRS.[35, 36]

Personalized prediction

Personalized medicine requires individualized prediction of treatment effect to guide shared decision-making. Using large databases, models can be developed that integrate patient and tumor characteristics with treatment effects to predict outcomes for various treatments for individual patients. The Cambridge Center for Risk Studies has developed such a model for breast cancer (www.breast.predict.nhs.uk).

Outline of this thesis

This thesis consists of three parts. In *Part I* the association of perioperative intra-arterial and systemic chemotherapy and survival after resection of CRLM is described. *Part II* is focused on trials in safety, feasibility, and efficacy of HAIP chemotherapy after resection of CRLM. In *Part III*, we discuss how patient- and disease-related factors are used for prognostication and prediction in patients with resectable CRLM.

Part I. Outcomes of perioperative intra-arterial and systemic chemotherapy
Part I aims to determine the effectiveness of perioperative chemotherapy in patients with resectable CRLM. In **Chapter 3** the effectiveness of different approaches of intra-arterial chemotherapy is evaluated in a systematic review and meta-analysis. **Chapter 4** is a retrospective analysis of the patterns of recurrence in patients treated with and without perioperative systemic chemotherapy. The aim was to evaluate if systemic chemotherapy converts the patterns of recurrence after resection. In **Chapter 5**, we performed a study to identify the impact of HAIP chemotherapy on the patterns of recurrence in patients treated with and without adjuvant HAIP chemotherapy. **Chapter 6** investigates the benefit of HAIP chemotherapy after resection or ablation of liver-only recurrent CRLM.

Part II. Clinical trials on intra-arterial pump chemotherapy
Part II describes two clinical trials on HAIP chemotherapy. HAIP chemotherapy is a complex treatment that requires expertise and skills of multidisciplinary team of surgical oncologist, medical oncologist, interventional radiologist, nuclear physicians, pharmacists, and oncology nurses. In **Chapter 7**, the results of a phase II safety and feasibility study of adjuvant HAIP chemotherapy in patients with resectable CRLM are evaluated. This study was followed by the phase III, randomized controlled trial developed to investigate the efficacy of HAIP chemotherapy after resection compared to resection alone in patients with resectable CRLM and a low CRS. The design of this study is evaluated in **Chapter 8**.

Part III. Prognostication and personalized treatment
In Part III several prognostic factors and models in the field of CRLM are studied. **Chapter 9** reports the results of a study in which we evaluated whether histopathological growth patterns (HGPs) of CRLM can predict the effectiveness of systemic chemotherapy after resection of CRLM. Finally, **Chapter 10** presents a prognostic model to predict 10-year OS for individual patients with resected CRLM based on patient, tumor, and treatment characteristics.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68(6):394-424.
2. Kankerregistratie N. www.iknl.nl/nkr-cijfers 2018.
3. Boussari O, Romain G, Remontet L, et al. A new approach to estimate time-to-cure from cancer registries data. *Cancer Epidemiol* 2018; 53:72-80.
4. Silversmit G, Jegou D, Vaes E, et al. Cure of cancer for seven cancer sites in the Flemish Region. *Int J Cancer* 2017; 140(5):1102-1110.
5. Renehan AG, Egger M, Saunders MP, et al. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *Bmj* 2002; 324(7341):813.
6. Margonis GA, Kim Y, Sasaki K, et al. Codon 13 KRAS mutation predicts patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Cancer* 2016; 122(17):2698-707.
7. Kim CG, Ahn JB, Jung M, et al. Effects of microsatellite instability on recurrence patterns and outcomes in colorectal cancers. *Br J Cancer* 2016; 115(1):25-33.
8. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; 244(2):254-9.
9. Weiss L, Grundmann E, Torhorst J, et al. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986; 150(3):195-203.
10. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
11. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4:283-301.
12. Ferrarotto R, Pathak P, Maru D, et al. Durable complete responses in metastatic colorectal cancer treated with chemotherapy alone. *Clin Colorectal Cancer* 2011; 10(3):178-82.
13. D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. *Ann Surg* 2015; 261(2):353-60.
14. Kingham TP, Correa-Gallego C, D'Angelica MI, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. *J Am Coll Surg* 2015; 220(4):471-9.
15. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. *J Clin Oncol* 1992; 10(6):896-903.

16. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18(16):2938-47.
17. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343(13):905-14.
18. Maiello E, Gebbia V, Giuliani F, et al. 5-Fluorouracil and folinic acid with or without CPT-11 in advanced colorectal cancer patients: a multicenter randomised phase II study of the Southern Italy Oncology Group. *Ann Oncol* 2000; 11(8):1045-51.
19. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22(2):229-37.
20. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351(4):337-45.
21. Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005; 23(15):3502-8.
22. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371(9617):1007-16.
23. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-1215.
24. Ychou M, Hohenberger W, Thezenas S, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. *Annals of Oncology* 2009; 20(12):1964-1970.
25. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; 27(8):1386-422.
26. Network NCC. www.nccn.org/professionals/physician_gls/default.aspx.
27. Snoeren N, van Hillegersberg R, Schouten SB, et al. Randomized Phase III Study to Assess Efficacy and Safety of Adjuvant CAPOX with or without Bevacizumab in Patients after Resection of Colorectal Liver Metastases: HEPATICA study. *Neoplasia* 2017; 19(2):93-99.
28. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; 15(6):601-11.

29. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. *Mol Cancer Ther* 2009; 8(5):1015-25.
30. Goere D, Benhaim L, Bonnet S, et al. 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* 2013; 257(1):114-20.
31. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.
32. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
33. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017:JCO2016718346.
34. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
35. Ayez N, van der Stok EP, Grunhagen DJ, et al. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol* 2015; 41(7):859-67.
36. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.

Chapter 2

Technical and oncological aspects of intra-arterial chemotherapy

Intra-arterial chemotherapy

The rational of adjuvant hepatic intra-arterial chemotherapy is that after liver resection about 50% of patients develop intrahepatic recurrences arising from micrometastases that were invisible at the time of liver resection.[1] CRLM mainly depend on arterial vasculature, while the normal liver parenchyma is mainly vascularized by the portal blood flow.[2]

The ideal drug for intra-arterial administration should have a high first-pass. Floxuridine (FUDR) is the preferred agent for intra-arterial chemotherapy using an implantable infusion pump because of its high hepatic extraction rate of 95%, resulting in a 400-fold increased intratumoral drug exposure, and minimal systemic toxicity.[3] In comparison, 5-FU has a hepatic extraction rate of less than 50%, allowing for only a 10-fold increased drug exposure by intra-arterial administration. Oxaliplatin has a similar hepatic extraction rate of about 50%, and a 5-fold increased drug exposure by intra-arterial administration.[3-5]

Intra-arterial chemotherapy requires insertion of a catheter in the hepatic artery. This can be accomplished with percutaneous insertion of a catheter in the femoral, intercostal, or brachial artery. The catheter is attached to a mediport and can be accessed percutaneously for connection with an external infusion pump. Percutaneous catheter insertion, however, has an increased risk of thrombosis because of a free-floating catheter in the hepatic artery, extrahepatic perfusion of chemotherapy, and infection.[6, 7] Furthermore, frequent hospital admissions are required for administration of chemotherapy. Percutaneous insertion of the catheter is mostly combined with 5-FU and oxaliplatin rather than floxuridine. Lorenz et al. compared adjuvant hepatic arterial infusion (HAI) chemotherapy (i.e., without an implantable pump) using 5-FU versus resection alone in CRLM patients.[8] The trial was prematurely closed after interim analysis for futility. At the time of interim analysis, 113 patients were randomized to each group in 26 centers; 21% of patients never started intra-arterial chemotherapy, and 63% of patients experienced severe (grade III or higher) chemotherapy related toxicities. This study demonstrated that a percutaneous approach using 5-FU is not feasible if simultaneously implemented in many centers, not safe, and not effective. Another study retrospectively compared 44 patients (all with 4 or more resected CRLM) that were treated with adjuvant HAI oxaliplatin plus systemic 5-FU with patients that were treated with systemic chemotherapy (FOLFOX or FOLFIRI). More than 84% of patients received more than 4 cycles and a superior 3-year DFS was found (33% vs. 5%, $p < 0.001$). HAI chemotherapy remained an independent prognostic factor for DFS in multivariable analysis (adjusted HR 0.37, 95% CI 0.23-0.60, $p < 0.001$).[9]

An alternative method involves surgical positioning of the intra-arterial catheter in the gastroduodenal artery in combination with a subcutaneous implantable pump (i.e., hepatic arterial infusion pump (HAIP) chemotherapy).[10] Because floxuridine has a short half-life, a pump is needed.[3] Implantable infusion pumps have been introduced in the late 1970s, and have the advantage of constant delivery of chemotherapy for longer periods in the outpatient

setting.[11] The infusion pumps are made of titanium, and have two chambers, one can be accessed percutaneously and filled with the drug, and the second is filled with pressurized gas that provides the mechanical energy for continuous infusion. No batteries are required. Surgical implantation of the catheter can be performed open or by a minimal-invasive robotic approach.[12]

The high exposure with floxuridine requires a prophylactic cholecystectomy to prevent chemical cholecystitis, and circumferential dissection of the entire GDA and proximal proper hepatic artery to avoid extrahepatic perfusion (i.e., pancreas, stomach, and duodenum) of floxuridine.[13] An early arterial phase CT angiography is mandatory to identify variant hepatic arterial anatomy. Replaced and accessory arteries should be ligated to achieve adequate bilobar perfusion through cross-perfusion in the liver.[14, 15]

Patients treated with adjuvant HAIP chemotherapy, receive chemotherapy administered in a 4-weeks-cycle, with a total of 6 cycles. The pump is filled with floxuridine for the first two weeks, followed by heparinized saline for two weeks. Liver function test are performed every two weeks. Chemical induced hepatitis (elevated AST and ALT) is reported in over 50% of patients, and is often mild. Strict adherence to the dose reduction schedules will resolve toxicity in most patients.[16] Intra-arterial chemotherapy is typically combined with systemic chemotherapy.

Possible complications of HAIP chemotherapy include extrahepatic perfusion, pump pocket infection, pump pocket hematoma, pump malfunction, arterial bleeding, arterial dissection, hepatic artery thrombosis, biliary sclerosis, and ulcer disease. Several precautions can minimize the risk of complications. An intra-operative methylene blue test and a postoperative Technetium-99-labeled macroaggregated albumin (Tc-99 m MAA) scintigraphy are performed to detect extrahepatic hepatic perfusion.[17] Extrahepatic perfusion of floxuridine may cause ulcer disease or pancreatitis. Biliary sclerosis is a late and severe complication of the toxic effect of floxuridine on the biliary tree and is typically avoided by dose reductions in patients with elevated liver enzymes. Rarely, patients require a biliary stent.[18] Concurrent infusion of dexamethasone and floxuridine has demonstrated to decrease the risk of biliary sclerosis.[19]

The NCCN guidelines recommend HAIP chemotherapy as an option in patients with resectable CRLM, but only in centers with extensive experience in both the surgical and medical oncologic aspects of the treatment.[20]

References

1. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
2. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; 30(5):969-77.
3. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983; 10(2):176-82.
4. Guthoff I, Lotspeich E, Fester C, et al. Hepatic artery infusion using oxaliplatin in combination with 5-fluorouracil, folinic acid and mitomycin C: oxaliplatin pharmacokinetics and feasibility. *Anticancer Res* 2003; 23(6D):5203-8.
5. Dzodic R, Gomez-Abuin G, Rougier P, et al. Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: comparative results with cisplatin using a rabbit VX2 tumor model. *Anticancer Drugs* 2004; 15(6):647-50.
6. Habbe TG, McCowan TC, Goertzen TC, et al. Complications and technical limitations of hepatic arterial infusion catheter placement for chemotherapy. *J Vasc Interv Radiol* 1998; 9(2):233-9.
7. Aldrighetti L, Arru M, Angeli E, et al. Percutaneous vs. surgical placement of hepatic artery indwelling catheters for regional chemotherapy. *Hepatogastroenterology* 2002; 49(44):513-7.
8. Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg* 1998; 228(6):756-62.
9. Goere D, Benhaim L, Bonnet S, et al. 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* 2013; 257(1):114-20.
10. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. *Mol Cancer Ther* 2009; 8(5):1015-1025.
11. Buchwald H, Grage TB, Vassilopoulos PP, et al. Intraarterial infusion chemotherapy for hepatic carcinoma using a totally implantable infusion pump. *Cancer* 1980; 45(5):866-9.
12. Qadan M, D'Angelica MI, Kemeny NE, et al. Robotic hepatic arterial infusion pump placement. *HPB (Oxford)* 2017; 19(5):429-435.
13. Ottery FD, Scupham RK, Weese JL. Chemical cholecystitis after intrahepatic chemotherapy. The case for prophylactic cholecystectomy during pump placement. *Dis Colon Rectum* 1986; 29(3):187-90.
14. Allen PJ, Stojadinovic A, Ben-Porat L, et al. The management of variant arterial anatomy during hepatic arterial infusion pump placement. *Ann Surg Oncol* 2002; 9(9):875-80.

15. Rayner AA, Kerlan RK, Stagg RJ, et al. Total hepatic arterial perfusion after occlusion of variant lobar vessels: implications for hepatic arterial chemotherapy. *Surgery* 1986; 99(6):708-15.
16. Doussot A, Kemeny NE, D'Angelica MI. Hepatic arterial infusional chemotherapy in the management of colorectal cancer liver metastases. *Hepat Oncol* 2015; 2(3):275-290.
17. Pelosi E, Masaneo I, Clara R, et al. Technetium-99m labelled macroaggregated albumin arterial catheter perfusion scintigraphy: prediction of gastrointestinal toxicity in hepatic arterial chemotherapy. *Eur J Nucl Med* 2000; 27(6):668-75.
18. Ammori JB, Kemeny NE. Regional hepatic chemotherapies in treatment of colorectal cancer metastases to the liver. *Semin Oncol* 2010; 37(2):139-48.
19. Kemeny N, Conti JA, Cohen A, et al. Phase II study of hepatic arterial floxuridine, leucovorin, and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 1994; 12(11):2288-95.
20. Network NCC. www.nccn.org/professionals/physician_gls/default.aspx.

Part I

Outcomes of perioperative intra-arterial and systemic chemotherapy

Chapter 3

Adjuvant intra-arterial chemotherapy for patients with resected colorectal liver metastases: a systematic review and meta-analysis

F.E. Buisman*, W.F. Filipe*, B. Galjart, D.J. Grünhagen, M.Y.V. Homs, A. Moelker, C. Verhoef, B. Groot Koerkamp

*Shared first authors

Accepted HPB 2021

Abstract

Background
The practice of adjuvant hepatic arterial infusion chemotherapy (HAIC) for colorectal liver metastasis (CRLM) varies widely. This systematic review and meta-analysis investigates the effectiveness of adjuvant HAIC and the influence of variations in HAIC treatment in patients with resected CRLM.

Methods
PRISMA guidelines were followed for this study. The search was limited to comparative studies (HAIC vs. no-HAIC) for overall survival. Subgroup meta-analyses using random-effects were performed for type of intra-arterial drug, method of catheter insertion, use of concomitant adjuvant systemic chemotherapy, and study design.

Results
Eighteen eligible studies were identified. After excluding overlapping cohorts, fifteen studies were included in the quantitative analysis, corresponding to 3584 patients. HAIC was associated with an improved overall survival (pooled hazard ratio (HR) 0.77, 95% CI 0.64-0.93). Survival benefit of HAIC was most pronounced in studies using floxuridine (pooled HR 0.76, 95% CI 0.62-0.94), surgical catheter insertion with a subcutaneous pump (pooled HR 0.71, 95% CI 0.61-0.84), and concomitant adjuvant systemic chemotherapy (pooled HR 0.75, 95% CI 0.59-0.96). The pooled HR of RCTs was 0.91 (95% CI 0.72-1.14), of which only 3 used floxuridine.

Discussion
Adjuvant HAIC is a promising treatment for patients with resectable CRLM, in particular HAIC with floxuridine using a surgically placed catheter with a subcutaneous pump, and concomitant systemic chemotherapy.

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer related death worldwide.[1] Synchronous and metachronous colorectal liver metastases (CRLM) account for 40% of all metastases in CRC patients. Resection and ablation are the only potentially curative treatments for CRLM, resulting in a 10-year survival rate of approximately 25%.[2, 3] However, 70% of patients develop recurrences after resection, with the liver being involved in the large majority of patients.[2, 4, 5]

Several therapies have been introduced to reduce disease recurrence and improve survival after curative treatment of CRLM. Perioperative systemic chemotherapy is widely administered.[6] Additionally, patients with resectable CRLM may benefit from adjuvant hepatic arterial infusion chemotherapy (HAIC).[7] This therapy is based on two main principles. First, CRLM, as opposed to normal liver parenchyma, primarily derive their blood supply from the hepatic artery rather than the portal vein.[8, 9] Second, systemic side effects of HAIC are limited due to the high first-pass effect in the liver of certain drugs (e.g., floxuridine and oxaliplatin), allowing for a high liver dosage.[10-12]

Several studies, including RCTs demonstrated promising survival benefits of adjuvant HAIC.[7] However, not all studies could confirm these findings, which may be a result of variations in intra-arterial drugs, method of drug delivery (surgical or percutaneous catheter insertion), and use of concomitant adjuvant systemic treatment.

The objective of this systematic review and meta-analysis was to investigate the effectiveness of adjuvant HAIC in patients with resected CRLM and the influence of variations in HAIC treatment.

Methods

Search strategy and study selection

The PRISMA guidelines were used to conduct this systematic review and meta-analysis.[13] A systematic search in Embase, Medline Ovid, Web of Science, Cochrane and Google Scholar was performed on April 13th 2021. A full description of the search is available in supplementary Table 1. Studies comparing overall survival (OS) in patients with and without HAIC after resection of CRLM were eligible. The search was restricted to articles written in English. Non-comparative and non-original studies (e.g., systematic reviews, meta-analyses) were excluded, as were studies not reporting OS. After removing duplicates, titles and abstracts were screened for eligibility by three independent researchers (FB, WF, BoG). Then full text articles were screened based on the inclusion and exclusion criteria. At each step, disagreement was resolved by consensus between two reviewers (FB, WF).

Data-extraction and qualitative assessment

Data were independently extracted by two reviewers (FB, WF). A standardized data extraction form was used. Patient characteristics, tumor characteristics, treatment characteristics of HAIC patient groups and comparative patient groups, and survival outcomes were extracted. When not reported, hazard ratios (HRs) with 95% confidence intervals (95% CIs) for OS were extracted from the Kaplan-Meier graphs and calculated using methods described by Tierney et al.[14] Quality assessment (Supplementary files) of the studies was performed using the RoB 2 (for randomized studies) and Newcastle Ottawa (for non-randomized studies).

Quantitative assessment

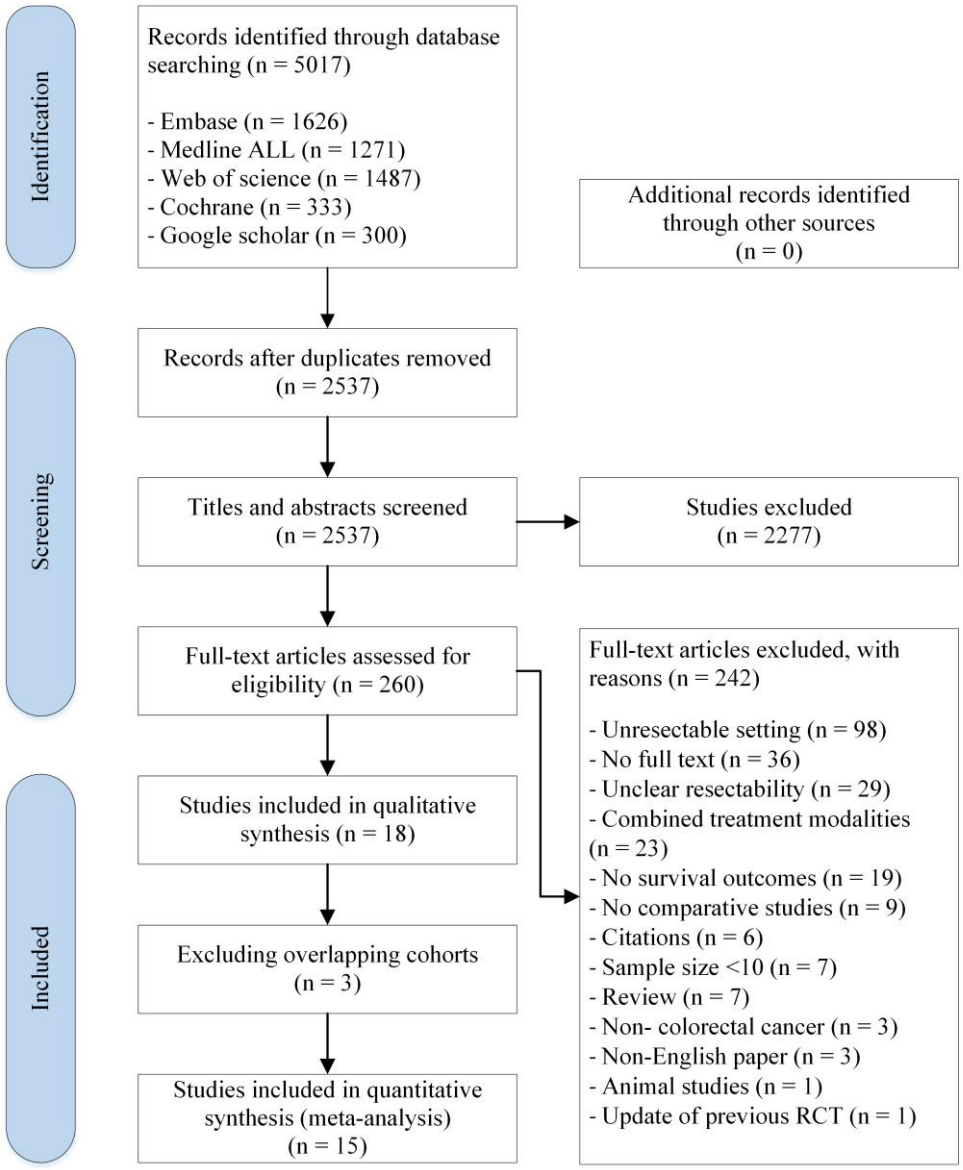
Random effects modelling was applied to create pooled estimates for OS. Heterogeneity was evaluated using the I^2 statistic. Forest plots and funnel plots (not shown) were created to display pooled OS estimates and the risk of publication bias, respectively. Subgroup analysis was performed for study design (RCT vs non-RCT), for the type of intra-arterial drug (floxuridine vs. other), the method of catheter insertion (surgical or subcutaneous), and the use of concomitant adjuvant systemic chemotherapy. Statistical analyses were performed using RevMan (Review Manager version 5.4.1).

Results

Study characteristics

After screening 2512 potentially relevant studies, the full-text of 260 studies was assessed for eligibility (Figure 1). Studies were primarily excluded when describing outcomes in patients with unresectable CRLM (n = 98) or when resectability status was unclear (n = 29). Full text was unavailable for 36 articles, none of which were RCTs (based on the abstract), and 29 articles (81%) were published before 1980. One study was excluded due to complete overlap of the cohort with another study.[15] Ultimately, eighteen studies were included, representing 2325 patients who received adjuvant HAIC and 3998 patients who did not.[5, 16-33] The number of patients treated with HAIC ranged between 5 and 785 across studies.

Figure 1. Prisma flowchart



Characteristics of the included studies are shown in Table 1.[5, 16-33] Eight studies were RCTs.[16, 17, 19, 21, 22, 26, 31, 32] Five studies included partially overlapping cohorts of patients.[5, 26, 27, 30, 33] Baseline patient and tumor characteristics are summarized in Table 2. Large variability between study cohorts was observed in terms of patient and tumor characteristics. Four studies included patients with (a history of) extrahepatic disease (EHD), ranging from 7% to 20% of the study population.[19, 29, 30]

Effectiveness of HAIC

For the quantitative assessment, 15 studies were included, representing 1391 patients treated with HAIC versus 2193 patients treated without HAIC after resection of CRLM.[16-24, 26, 28-32] Four studies have been performed in Memorial Sloan Kettering Cancer Center (MSKCC) and had overlapping cohorts [5, 26, 27, 30, 33]; the largest study was selected for quantitative assessment.[30] The pooled HR (Figure 2a) for OS for all studies was 0.77 (95% CI 0.64-0.93). Moderate heterogeneity, in terms of the effectiveness of HAIC, was present with an I^2 of 37%. When evaluating the eight RCTs (Figure 2b), representing 312 HAIC patients and 340 patients without HAIC, the pooled HR was 0.91 (95% CI 0.72-1.14, $I^2 = 0\%$).[7, 16, 17, 19, 22, 26, 31, 32]

Figure 2a. Forest plot overall survival all studies

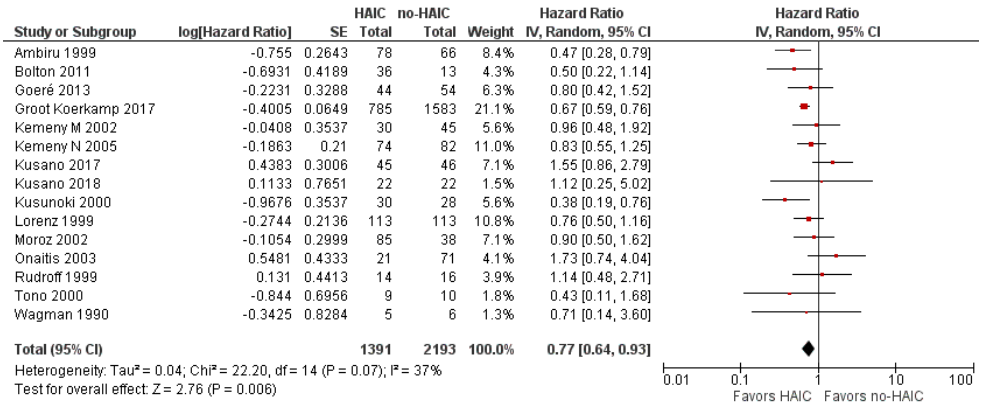
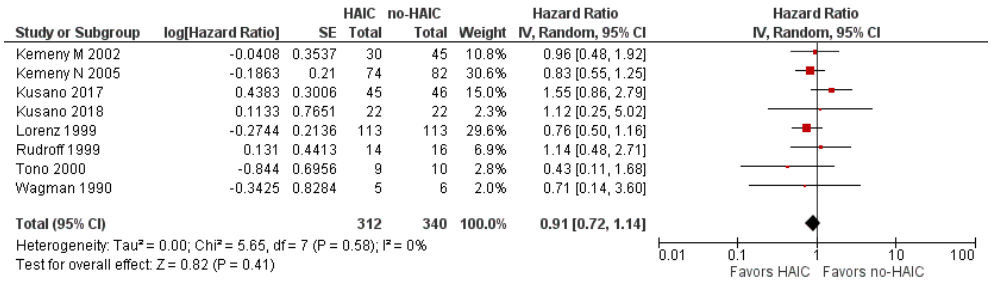


Figure 2b. Forest plot overall survival RCT's only



HAIC agents

Floxuridine was used as primary HAIC agent in seven studies (including three RCTs), representing 1036 HAIC patients (vs. 1838 no-HAIC patients), and was infused continuously using a surgically placed catheter and subcutaneous infusion pump or port.[16, 22-24, 26, 28, 30] Patients were scheduled to receive six cycles of 12 to 14 days of continuous HAIC with floxuridine at a dosage of 0.1 to 0.5 mg/kg/day or 0.2-0.3/m^2/day followed by 12 or 14 days of saline.[16, 22-24, 26, 28, 30] The pooled HR of studies using floxuridine as the primary HAIC agent was 0.76 (95% CI 0.62-0.94, I^2 = 21%) in favor of HAIC (Figure 3). Eight studies (including five RCTs) administered intra-arterial drugs other than floxuridine and represented 355 HAIC and 355 no-HAIC patients [17-21, 29, 31, 32]; seven studies administered intra-arterial 5-FU [17-21, 31, 32] and in one study intra-arterial oxaliplatin was used.[29] Intra-arterial 5-FU was delivered continuously using a subcutaneous infusion pump or port [17, 18, 21] or with bolus injections.[19, 20, 29, 31, 32] In two studies, patients also received intra-arterial Mitomycine C with or without aclarubicine.[18, 19] HAIC with oxaliplatin was used in one study. The pooled HR of studies using intra-arterial 5-FU or oxaliplatin (Figure 3) was 0.74 (95% CI 0.52-1.06, I^2 = 52%).

Table 1. Study characteristics

Author	Inclusion period	Center	Catheter implantation	Infusion rate	HAIC agent	Concomitant adj. systemic	Comparative cohort
RCT							
Wagman	1982-1986	City of Hope	Surgical	Cont.	FUDR	None	None
Lorenz	1991-1996	JW Goethe-University	Surgical	Cont. 4. days	5-FU/FA	None	None
Rudroff	1984-1985	Friedrich Schiller	Surgical	Bolus 4 hours	5-FU/MMC	None	None
Tono	1993-1995	Osaka Hospital	Surgical	Cont. 5 days	5-FU	5-FU	5-FU
Kemeny M	1990-1997	Multicenter	Surgical	Cont. 14 days	FUDR	5-FU	None
Kemeny N	1991-1999	MSKCC	Surgical	Cont. 14 days	FUDR	5-FU/LV	5-FU/LV
Kusano 2017	2000-2003	Kushiro Rosai Hosp.	Percutaneous	Bolus 24h	5-FU	UFT/LV	UFT/LV
Kusano 2018	2005-2007	Kushiro Rosai Hosp.	Percutaneous	Bolus 24h	5-FU	UFT/LV	UFT/LV
Non-RCT							
Ambiru	1984-1998	Chiba University	Surgical	Cont. 14 days	5-FU/MMC/ACR	5-FU	None
Kusunoki	1990-1995	Hyogo Medicine	Surgical	Unspecified	5-FU	UFT	UFT
Moroz	1989 -1999	Royal Perth Hospital	Surgical	Cont.12 days	FUDR +/- LV	None	None
Onaitis	NR	Duke University MC	Surgical	Cont.14 days	FUDR	Various	Various
Bolton	1993-1999	Mayo Clinic Roch.	Surgical	Cont.14 days	FUDR	5-FU/LV	None
House	2000-2005	MSKCC	Surgical	Cont.14 days	FUDR	IRINO/OXA	IRINO/OXA
Goéré	2000-2009	Gustave Roussy	Surgical*	Bolus 2 hours	OXA	5-FU/LV	FOLF(OX/IRI)
Groot Koerkamp	1992-2012	MSKCC	Surgical	Cont.14 days	FUDR	Various	Various
Buisman	1991-2012	Multicenter	Surgical	Cont.14 days	FUDR	FOLF(OX/IRI)	FOLF(OX/IRI)
Srouji	2000-2007	MSKCC	Surgical	Cont.14 days	FUDR	Various	Various

Abbreviations: ACR: aclarubicin, Adj: adjuvant, Cont: continuous, 5-FU: 5-Fluorouracil, FA: Folinic acid, FOLFOX: Folinic acid/Leucovorin/Oxaliplatin, FOLFIRI: Folinic acid/Leucovorin/Irinotecan, FUDR: Floxuridine, HAIC: hepatic arterial infusion chemotherapy, LV: Leucovorin, MMC: Mitomycin C, MSKCC: Memorial Sloan Kettering Cancer Center, NR: not reported, OXA: Oxaliplatin, RCT: randomized controlled trial, UFT: Tegafur/uracil, IRINO: Irinotecan.
*79% surgical, 21% percutaneous

Table 2. Baseline characteristics of HAIC patient group

Author	HAIC	no-HAIC	Follow-up (m)	Age (y)	N+ CRC	Syn.	No. CRLM	CRLM size (cm)	CEA preop.	Prior SYS	EHD
	n	*n*	*median*	*median (r)*	*n (%)*	*n (%)*	*median (r)*	*median (r)*	*median (r)*	*n (%)*	*n (%)*
RCT											
Wagman	5	6	NR	61 (43-74)	9 (56)	9 (56)	2 (1-7)	NR	NR	NR	0
Lorenz	113	113	≥ 18	61 (30-76)	53 (50)	34 (32)	NR	NR	NR	NR	0
Rudroff	14	16	NR	58 (39-70)	14 (100)	6 (46)	NR	4.5 (1-13)	NR	NR	1 (7)
Tono	9	10	62.2	59 (± 5.8)	2 (22)	4 (44)	> 1, 3 (33%)	26.3 (± 15)	NR	NR	NR
Kemeny M	30	45	51	62 (29-78)	NR	9 (30)	NR	NR	NR	16 (53)	0
Kemeny N	74	82	123	59 (28-79)	NR	23 (31)	NR	NR	11.5 (19-259)	39 (53)	0
Kusano 2017	45	46	66	63 (40-80)	NR	15 (33)	>5,n=3, 7%	≥4, n=12	NR	0	0
Kusano 2018	22	22	19.9	62 (45-78)	NR	10 (46)	>6,n=3,14%	≥4, n=7	NR	8 (36)	0
Non-RCT											
Ambiru	78	66	NR	63 (21-80)	NR	31 (40)	NR	NR	NR	NR	0
Kusunoki	30	28	60	60 (25-71)	NR	12 (40)	≥4cm, n=3	2.5 (1-10)	12 (1-1020)	7 (23)	0
Moroz	85	38	NR	NR	NR	NR	NR	NR	NR	NR	0
Onaitis	21	71	29	53, SD=11	12 (21)	NR	1.8 (mean)	2.2 (mean)	114 (mean)	NR	0
Bolton	36	13	NR	62 (25-75)	NR	NR	4.0 (0-10)	NR	NR	NR	0
House	125	125	43	55 (28-80)	84 (68)	NR	2.0 (1–10)	2.8 (0.2–17)	12 (1-1235)	69 (55)	0
Goéré	44	54	60	55 (SD=8)	30 (68)	38 (86)	> 6, 35 (80)	2.9 (2-4)	4 (3-10)	44(100)	9(20)
Gr. Koerkamp	785	1583	55	56 (SD=12)	905 (65)	468 (60)	3.5 (NR)	3.9 (NR)	> 200 n=57	NR	42(5)
Buisman	601	1527	96	57 (49–66)	371 (62)	432	NR	>5 cm: 360	>200: 131	441(73)	0
Srouji	208	153	142	59 (26-96)	120 (58)	NR	2 (1-9)	3 (0.3-20)	8.4 (1-12325)	157(76)	0

Abbreviations: CEA: carcinoembryonic antigen, CRC: colorectal cancer, CRLM: colorectal liver metastasis, EHD: extrahepatic disease, HAIC: hepatic arterial infusion chemotherapy, N+: positive nodal status, NR: not reported; r: range, SD: standard deviation, SYN: synchronous, SYS: systemic chemotherapy, Preop: preoperative.

Catheter insertion technique

Thirteen studies used a surgically placed catheter, corresponding to 1324 HAIC patients and 2125 no-HAIC patients.[16-24, 26, 28-30] A catheter was secured in the gastroduodenal artery (GDA) with the tip at hepatic artery. The catheter was then connected to a subcutaneous infusion pump or port that can be accessed percutaneously for drug delivery. The pooled HR of studies using surgically placed catheters for HAIC was 0.71 (95% 0.61-0.84, I^2 = 19%), which represented 1325 HAIC patients and 2124 no-HAIC patients (Figure 3).

Two studies, representing 67 HAIC patients and 68 no-HAIC patients, used a percutaneous intra-arterial catheter .[31, 32] The HAI catheter was inserted via the femoral or subclavian artery. A catheter with a side hole was positioned and fixed with the tip of the catheter in the GDA such that the side hole lies at the arterial flow towards the liver. The GDA, right gastric artery, and aberrant or accessory hepatic arteries were embolized to prevent extrahepatic perfusion via the catheter. The pooled HR of studies applying a percutaneous approach (Figure 3) for HAIC was 1.48 (0.86-2.57, I^2 = 0%).

Concomitant adjuvant systemic chemotherapy

Concomitant adjuvant systemic chemotherapy included any combination of 5-FU, oxaliplatin and irinotecan and was administered during HAIC in 11 studies representing 1174 HAIC and 2020 no-HAIC patients.[18, 20-22, 24, 25, 28-32] The pooled HR for OS was 0.75 (95% CI 0.59-0.96, I^2 = 50%), in favor of HAIC (Figure 3). In four adjuvant HAIC studies, representing 218 HAIC and 172 no-HAIC patients, no concomitant adjuvant systemic chemotherapy was administered.[16, 17, 19, 23] The pooled HR for OS 0.84 (95% CI 0.61-1.14, I^2 = 0%) (Figure 3).

Figure 3a. Forest plot for overall survival for floxuridine studies only

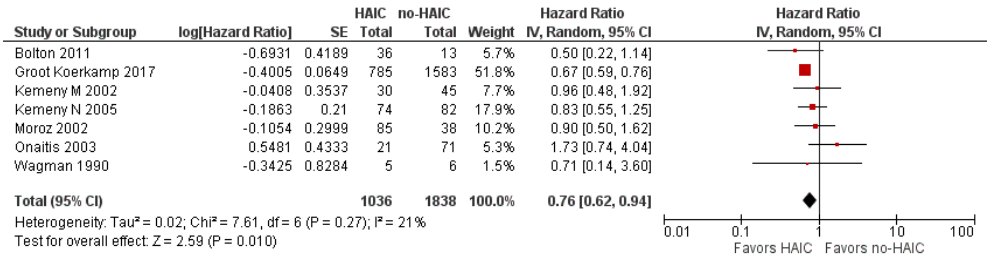


Figure 3b. Forest plot for overall survival for other HAIC agents only

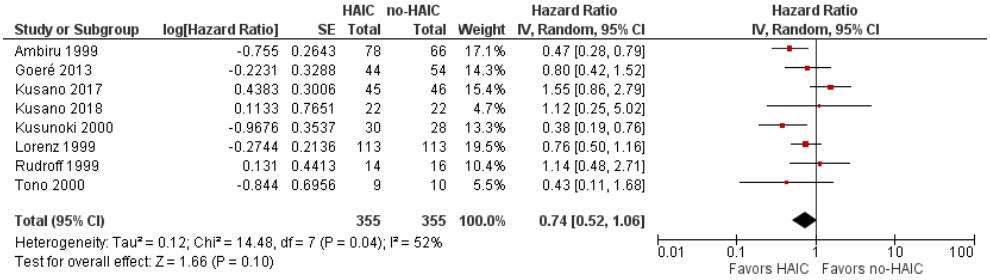


Figure 3c. Forest plot for overall survival for surgical HAIC catheter insertion only

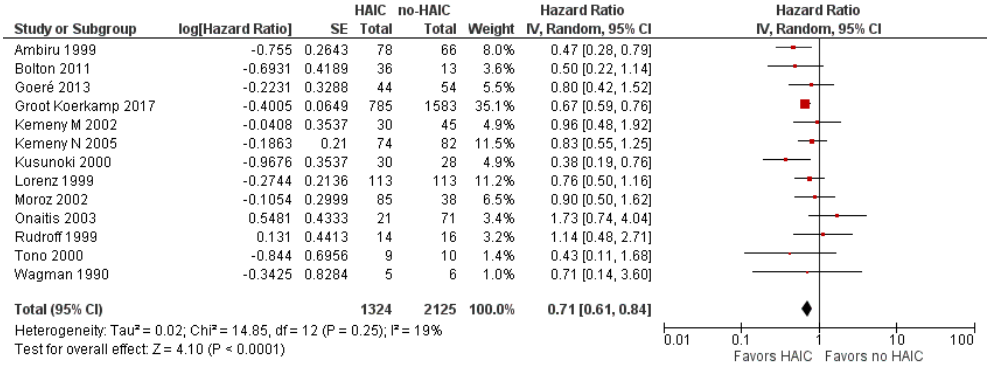


Figure 3d. Forest plot for overall survival for percutaneous HAIC catheter insertion only

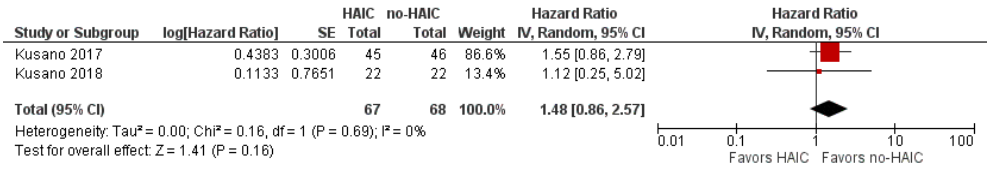


Figure 3e. Forest plot for overall survival for HAIC with concomitant systemic chemotherapy only

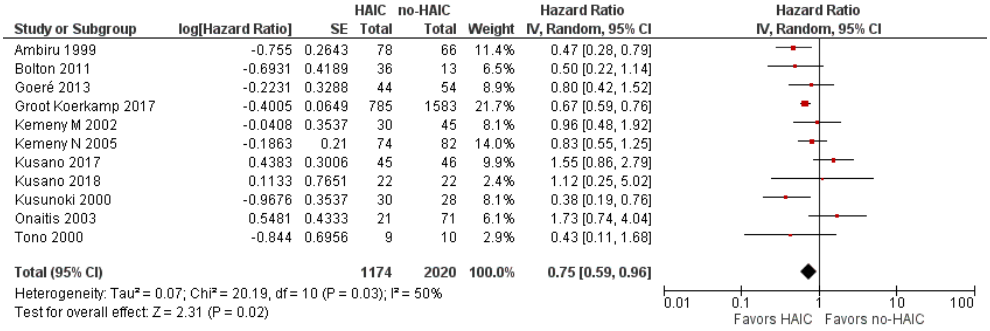
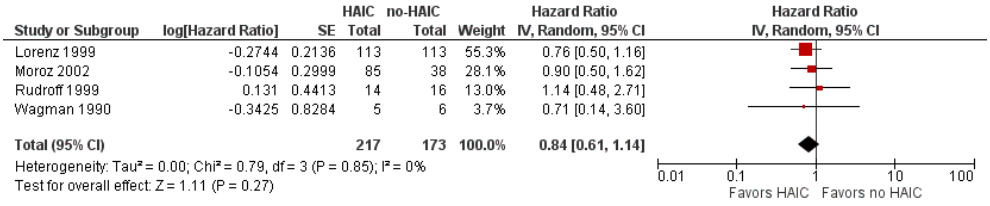


Figure 3f. Forest plot for overall survival for HAIC without concomitant chemotherapy only



Discussion

The pooled HR for OS of patients who underwent adjuvant HAIC after resection of colorectal liver metastases was better than without adjuvant HAIC (pooled HR 0.77, 95% CI 0.64-0.93). Survival benefit of HAIC was best in studies using floxuridine (pooled HR 0.76, 95% CI 0.62-0.94), surgical catheter insertion (pooled HR 0.71, 95% CI 0.61-0.84), and concomitant adjuvant systemic chemotherapy (pooled HR 0.75, 95% CI 0.59-0.96).

Pooled analysis of only RCTs failed to demonstrate an OS benefit in favor of HAIC (HR 0.91 95% CI 0.72-1.14). However, these RCTs were heterogeneous regarding intra-arterial drug, method of catheter insertion, and concomitant adjuvant systemic chemotherapy. In particular, five RCTs administered intra-arterial 5-FU of which 4 were terminated prematurely due to lack of effectiveness or low accrual.[16, 17, 19, 23] The largest completed RCT used intra-arterial floxuridine with a surgically placed catheter and subcutaneous pump.[26] Median progression-free survival was 31.3 months in the HAIC group versus 17.2 months in the no-HAIC group ($p = 0.02$); median OS was 68.4 months in the HAIC group versus 58.8 months in the no-HAIC group ($p = 0.10$), with ten-year OS of 41.1% versus 27.3%. Of note, this is the only large RCT that completed accrual. In a previous meta-analyses of seven RCTs, Nelson et al. could not demonstrate a difference in OS for adjuvant HAIC (HR 1.09, 95% CI 0.89-1.34).[34] The present study included one additional RCT and long-term results of the largest RCT. Liu et al. identified nine randomized and non-randomized studies with a pooled HR for OS of 0.75 (95% CI 0.56–0.99) in favor of HAIC.[35] However, this study included several overlapping cohorts and 5 more recent studies were not included. Additional adequately powered RCTs are needed to investigate whether HAIC can improve survival.

Zhang et al. recently published a systematic review in which a pooled analysis of seven RCTs showed a HR of 0.63 (95% CI 0.56–0.99), significantly in favor of adjuvant HAIC with respect to no adjuvant HAIC.[36] However, two articles were incorrectly added to the analysis; one article analyses HAIC in the palliative setting for CRLM (without resection) [20], the other article was not a RCT.[37] To our knowledge, no previous published article addresses heterogeneity of treatment with HAIC and by analyzing subgroups based on treatment approach of HAIC.

In subgroup analysis for different intra-arterial chemotherapeutics, floxuridine-based studies found an improvement in OS in favor of HAIC (HR 0.76, 95% CI 0.62-0.94), while this could not be demonstrated for 5-FU and oxaliplatin-based studies (HR 0.74, 95% CI 0.52-1.06). Oxaliplatin, however, was evaluated in only one retrospective study.[29] The rationale behind the superior effectiveness of HAIC with floxuridine is the high hepatic extraction rate of 95% allowing for high intra-arterial dosages in the liver resulting in a tumor exposure 400 times greater than achieved with systemic administration with limited systemic side-effects.[10] 5-FU and oxaliplatin have a hepatic first-pass effect of about 50% [11, 38], allowing for a 5 to 10-fold increased drug exposure in the liver tumor, compared with systemic administration.[10, 11,

[39] Of note, the pooled HR of the non-floxuridine studies is similar to that of the floxuridine studies, but with a wider confidence interval, possibly corresponding to a smaller pooled sample size rather than a less effective treatment. However, based on pharmacodynamics and pooled analysis of survival data, floxuridine should be investigated in future RCTs. Floxuridine has been FDA approved since 1971, but is not yet registered in the Europe.

In the majority of studies the intra-arterial catheter was primarily inserted surgically.[16-25, 28-30] The pooled analysis of studies using this method showed a survival benefit in favor of HAIC (HR 0.71, 95% CI 0.61-0.84). Two studies administered HAIC via a percutaneously inserted catheter with a pooled HR of 1.48 (95% CI 0.86-2.57). The percutaneous approach to HAIC catheter implantation has been largely abandoned due to the challenging procedure and high complication rate, in particular, hepatic artery thrombosis and catheter dislodgement with extrahepatic perfusion.[29, 40-45] However, technical advancements in percutaneous catheter implantation may reduce complications.[46] Based on the currently published results, future RCTs should use a surgically placed catheter with a subcutaneous infusion pump.

HAIC has been mostly administered as an addition to the standard of care of adjuvant systemic chemotherapy. Subgroup analyses found improved survival of HAIC when administered with concomitant systemic chemotherapy (HR 0.75, 95% CI 0.59-0.96), while this could not be demonstrated in older studies without concomitant systemic chemotherapy (HR 0.84, 95% CI 0.61-1.14). On the other hand, a systematic review of RCTs could not demonstrate an improved OS associated with perioperative systemic chemotherapy in the treatment of resectable CRLM compared with resection alone.[6] A synergistic effect of HAIC and systemic chemotherapy cannot be ruled out and should be investigated in future RCTs.

HAIC is a liver directed therapy and should therefore be directed at patients at risk of hepatic recurrence after resection of CRLM. The challenge lies in differentiating patients likely to develop hepatic recurrence, from patients that are likely to either be cured without HAIC (about 20%) or develop extrahepatic recurrence (about 50%).[2, 5] The former represents patients that would not benefit from HAIC, as they are cured regardless of HAIC. The latter group would be unlikely to benefit from HAIC, as the liver directed treatment does not protect against initial extrahepatic recurrence. Therefore, future studies should find biomarkers to predict whether patients will develop initial extrahepatic recurrence.

The present study has several limitations. The results of the meta-analysis in this study are limited due to the poor quality of the retrospective studies and small sample size of the RCTs. The included studies varied substantially in treatment approach, requiring subgroup analysis with small cumulative sample size. Moreover, systemic oxaliplatin- or irinotecan-based chemotherapy constitutes the standard of treatment in many countries, but was not administered in any of the included RCTs and only in the more recent retrospective studies. The vast majority of patients were included one or two decades prior to the writing of this meta-analysis. Therefore, prognostic biomarkers, such as sidedness of the primary CRC, tumoral mutational status (e.g., KRAS and BRAF) and histological growth patterns were not

considered in the included studies.[47-51] On the other hand, two recent studies showed that sidedness and genomic alterations in KRAS did not influence the effectiveness of adjuvant HAIC.[52, 53] Also, most research on HAIC originates from only few centers which could impair the generalizability of the results found in this study.

An RCT that is adequately powered to detect a clinically relevant difference in OS is warranted to determine whether adjuvant HAIC after resection of CRLM provides an OS benefit. The PUMP trial (NTR7493) is an ongoing multicenter phase-III RCT in the Netherlands, in which patients are randomized between resection and resection followed by six cycles of adjuvant continuous HAIC with floxuridine via a surgically implanted catheter and infusion pump.[54, 55] In this trial, 230 patients with resectable CRLM and a low clinical risk score (CRS) in the Netherlands are needed.[54] This patient selection was based on the finding that in particular low CRS seemed to benefit from HAIC floxuridine.[30] The PACHA trial (NCT02494973) is accruing 220 patients with at least four CRLM, thus targeting high-risk patients. In this phase II/III trial patients are randomized between adjuvant HAI oxaliplatin via a percutaneously or surgically implanted HAIC catheter and systemic 5-FU and leucovorin or adjuvant systemic chemotherapy with FOLFOX. The authors suggested HAIC should be reserved for high-risk patients due the high technicality of the treatment. Results of the PUMP and PACHA trials may determine the role of adjuvant HAIC in patients with resectable CRLM [56]. Future RCTs should also confirm the promising results of HAIC in the setting of unresectable CRLM with a response rate up to 85% in pretreated patients.[57]

HAIC has been performed since the 1980s in MSKCC and only a few other centers. Why has it not gained further foothold across the world? Firstly, the promising results of the initial RCT's were published at a time when oxaliplatin and irinotecan were introduced. Both were effective in the setting of unresectable metastatic colorectal cancer. With these new treatments, it appeared that HAIC was not needed anymore. Only many years later, it was shown that oxaliplatin and irinotecan do not improve OS in the perioperative setting.[58, 59] Moreover, many other systemic drugs were anticipated, but did not materialize in the adjuvant setting. Secondly, floxuridine is not registered the EU. The incentive for the pharmaceutical industry to register floxuridine has been low with a price of about 75 USD for one vial. The registration process of a drug in the EU is expensive. We are currently exploring registration of floxuridine in the EU in collaboration with the pharmaceutical industry. Thirdly, HAIC requires a continuous infusion pump for drug delivery, because the half-life of floxuridine is less than 10 minutes. No infusion pump with the intended use of intra-arterial chemotherapy is currently registered in the EU. The Codman pump that has been used in the USA contains freon gas that is banned from the EU for environmental reasons. Finally, a considerable hurdle for dissemination is that HAIC is a complex multidisciplinary treatment that requires experience and skills.

In conclusion, adjuvant HAIC was associated with better survival in patients with resectable CRLM, in particular for HAIC with floxuridine using a surgically placed catheter and subcutaneous pump, and concomitant systemic chemotherapy.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68(6):394-424.
2. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
3. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? *Surgery* 2018; 163(6):1238-1244.
4. Buisman FE, Galjart B, van der Stok EP, et al. Recurrence Patterns After Resection of Colorectal Liver Metastasis are Modified by Perioperative Systemic Chemotherapy. *World J Surg* 2020; 44(3):876-886.
5. Buisman FE, Galjart B, van der Stok EP, et al. The impact of hepatic arterial infusion pump chemotherapy on hepatic recurrences and survival in patients with resected colorectal liver metastases. *HPB (Oxford)* 2019.
6. Khoo E, O'Neill S, Brown E, et al. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. *HPB (Oxford)* 2016; 18(6):485-93.
7. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *New Engl J Med* 1999; 341(27):2039-2048.
8. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; 30(5):969-77.
9. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 1974; 75(4):589-96.
10. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983; 10(2):176-82.
11. Guthoff I, Lotspeich E, Fester C, et al. Hepatic artery infusion using oxaliplatin in combination with 5-fluorouracil, folinic acid and mitomycin C: oxaliplatin pharmacokinetics and feasibility. *Anticancer Res* 2003; 23(6D):5203-8.
12. Dzodic R, Gomez-Abuin G, Rougier P, et al. Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: comparative results with cisplatin using a rabbit VX2 tumor model. *Anticancer Drugs* 2004; 15(6):647-50.
13. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6(7):e1000097.
14. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; 8:16.

15. Sadot E, Groot Koerkamp B, Leal JN, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? *Ann Surg* 2015; 262(3):476-85; discussion 483-5.
16. Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. *J CLIN ONCOL* 1990; 8(11):1885-1893.
17. Lorenz M, Müller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. *Ann Surg* 1998; 228(6):756-762.
18. Ambiru S, Miyazaki M, Ito H, et al. Adjuvant regional chemotherapy after hepatic resection for colorectal metastases. *Br J Surg* 1999; 86(8):1025-1031.
19. Rudroff C, Altendorf-Hoffmann A, Stangl R, et al. Prospective randomised trial on adjuvant hepatic-artery infusion chemotherapy after RO resection of colorectal liver metastases. *Langenbeck's Arch Surg* 1999; 384(3):243-249.
20. Kusunoki M, Yanagi H, Noda M, et al. Results of pharmacokinetic modulating chemotherapy in combination with hepatic arterial 5-fluorouracil infusion and oral UFT after resection of hepatic colorectal metastases. *Cancer* 2000; 89(6):1228-1235.
21. Tono T, Hasuike Y, Ohzato H, et al. Limited but definite efficacy of prophylactic hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases: A randomized study. *Cancer* 2000; 88(7):1549-56.
22. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: Surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy - An intergroup study. *J Clin Oncol* 2002; 20(6):1499-1505.
23. Moroz P, Salama PR, Gray BN. Resecting large numbers of hepatic colorectal metastases. *ANZ J Surg* 2002; 72(1):5-10.
24. Onaitis M, Morse M, Hurwitz H, et al. Adjuvant hepatic arterial chemotherapy following metastasectomy in patients with isolated liver metastases. *Ann. Surg.* 2003; 237(6):782-789.
25. Martin RC, Edwards MJ, McMasters KM. Morbidity of adjuvant hepatic arterial infusion pump chemotherapy in the management of colorectal cancer metastatic to the liver. *Am J Surg* 2004; 188(6):714-721.
26. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
27. House MG, Kemeny NE, Gönen M, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. *Ann Surg* 2011; 254(6):851-856.
28. Bolton JS, O'Connell MJ, Mahoney MR, et al. Hepatic arterial infusion and systemic chemotherapy after multiple metastasectomy in patients with colorectal carcinoma metastatic to the liver: A North Central Cancer Treatment Group (NCCTG) phase II study, 92-46-52. *Clin Colorectal Cancer* 2012; 11(1):31-37.

29. Goéré D, Benhaim L, Bonnet S, et al. 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* 2013; 257(1):114-120.
30. Koerkamp BG, Sadot E, Kemeny NE, et al. Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: A propensity score analysis. *J Clin Oncol* 2017; 35(17):1938-1944.
31. Kusano M, Honda M, Okabayashi K, et al. Randomized controlled Phase III study comparing hepatic arterial infusion with systemic chemotherapy after curative resection for liver metastasis of colorectal carcinoma: JFMC 29-0003. *J Cancer Res Ther* 2017; 13(1):84-90.
32. Kusano M, Aoyama T, Okabayashi K, et al. A randomized phase III study of hepatic arterial infusion chemotherapy with 5-fluorouracil and subsequent systemic chemotherapy versus systemic chemotherapy alone for colorectal cancer patients with curatively resected liver metastases (Japanese Foundation for Multidisciplinary Treatment of Cancer 32). *J Cancer Res Ther* 2018; 14(10):S761-S766.
33. Srouji R, Narayan R, Boerner T, et al. Addition of adjuvant hepatic artery infusion to systemic chemotherapy following resection of colorectal liver metastases is associated with reduced liver-related mortality. *J Surg Oncol* 2020; 121(8):1314-1319.
34. Nelson R, Freels S. Hepatic artery adjuvant chemotherapy for patients having resection or ablation of colorectal cancer metastatic to the liver. *Cochrane Database Syst Rev* 2006(4):CD003770.
35. Liu W, Song QK, Xing BC. A systematic review and meta-analysis to reappraise the role of adjuvant hepatic arterial infusion for colorectal cancer liver metastases. *Int J Colorectal Dis* 2015; 30(8):1091-102.
36. Zhang Y, Wang K, Yang T, et al. Meta-Analysis of Hepatic Arterial Infusion for Liver Metastases From Colorectal Cancer. *Front Oncol* 2021; 11:628558.
37. Ghiringhelli F, Vincent J, Bengrine L, et al. Hepatic arterial chemotherapy with raltitrexed and oxaliplatin versus standard chemotherapy in unresectable liver metastases from colorectal cancer after conventional chemotherapy failure (HEARTO): a randomized phase-II study. *J Cancer Res Clin Oncol* 2019; 145(9):2357-2363.
38. Ranieri G, Laforgia M, Nardulli P, et al. Oxaliplatin-Based Intra-arterial Chemotherapy in Colo-Rectal Cancer Liver Metastases: A Review from Pharmacology to Clinical Application. *Cancers (Basel)* 2019; 11(2).
39. Stratmann SL. Hepatic artery chemotherapy in the management of colorectal metastases. *Proc (Bayl Univ Med Cent)* 2002; 15(4):376-9.
40. Clouse ME, Ahmed R, Ryan RB, et al. Complications of long term transbrachial hepatic arterial infusion chemotherapy. *AJR Am J Roentgenol* 1977; 129(5):799-803.

41. Herrmann KA, Waggershauser T, Sittek H, et al. Liver intraarterial chemotherapy: use of the femoral artery for percutaneous implantation of catheter-port systems. *Radiology* 2000; 215(1):294-9.
42. Oi H, Kishimoto H, Matsushita M, et al. Percutaneous implantation of hepatic artery infusion reservoir by sonographically guided left subclavian artery puncture. *AJR Am J Roentgenol* 1996; 166(4):821-2.
43. Petrek JA, Minton JP. Treatment of hepatic metastases by percutaneous hepatic arterial infusion. *Cancer* 1979; 43(6):2182-8.
44. Seki H, Kimura M, Yoshimura N, et al. Hepatic arterial infusion chemotherapy using percutaneous catheter placement with an implantable port: assessment of factors affecting patency of the hepatic artery. *Clin Radiol* 1999; 54(4):221-7.
45. Wacker FK, Boese-Landgraf J, Wagner A, et al. Minimally invasive catheter implantation for regional chemotherapy of the liver: a new percutaneous transsubclavian approach. *Cardiovasc Intervent Radiol* 1997; 20(2):128-32.
46. Deschamps F, Rao P, Teriitehau C, et al. Percutaneous femoral implantation of an arterial port catheter for intraarterial chemotherapy: feasibility and predictive factors of long-term functionality. *J Vasc Interv Radiol* 2010; 21(11):1681-8.
47. Yaeger R, Cercek A, Chou JF, et al. BRAF mutation predicts for poor outcomes after metastasectomy in patients with metastatic colorectal cancer. *Cancer* 2014; 120(15):2316-24.
48. Brudvik KW, Kopetz SE, Li L, et al. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. *Br J Surg* 2015; 102(10):1175-83.
49. Schirripa M, Cremolini C, Loupakis F, et al. Role of NRAS mutations as prognostic and predictive markers in metastatic colorectal cancer. *Int J Cancer* 2015; 136(1):83-90.
50. Margonis GA, Buettner S, Andreatos N, et al. Association of BRAF Mutations With Survival and Recurrence in Surgically Treated Patients With Metastatic Colorectal Liver Cancer. *JAMA Surg* 2018; 153(7):e180996.
51. Galjart B, Nierop PMH, van der Stok EP, et al. Angiogenic desmoplastic histopathological growth pattern as a prognostic marker of good outcome in patients with colorectal liver metastases. *Angiogenesis* 2019; 22(2):355-368.
52. Gholami S, Stewart S, Kemeny N, et al. Impact of Primary Tumor Laterality on Adjuvant Hepatic Artery Infusion Pump Chemotherapy in Resected Colon Cancer Liver Metastases: Analysis of 487 Patients. *Ann Surg Oncol* 2021; 28(7):3685-3694.
53. Gholami S, Kemeny NE, Boucher TM, et al. Adjuvant Hepatic Artery Infusion Chemotherapy is Associated With Improved Survival Regardless of KRAS Mutation Status in Patients With Resected Colorectal Liver Metastases: A Retrospective Analysis of 674 Patients. *Ann Surg* 2020; 272(2):352-356.
54. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
55. Buisman FE, Homs MYV, Grünhagen DJ, et al. 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* 2019; 19(1):327.

56. Goéré D, Pignon JP, Gelli M, et al. 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* 2018; 18(1):787.
57. Datta J, Narayan RR, Kemeny NE, et al. Role of Hepatic Artery Infusion Chemotherapy in Treatment of Initially Unresectable Colorectal Liver Metastases: A Review. *JAMA Surg* 2019; 154(8):768-776.
58. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371(9617):1007-16.
59. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-1215.

Supplementary Table 1. Search strategy: April 13, 2021

Hepatic arterial infusion colorectal liver metastasis

Database searched	via	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 -	1626	1597
Medline ALL	Ovid	1946 -	1271	161
Web of Science Core Collection	Web of Knowledge	1975 -	1487	502
Cochrane Central Register of Controlled Trials	Wiley	1992 -	333	195
Other sources: Google Scholar (300 top ranked)			300	82
Total			**5017**	**2537**

Embase.com

((('hepatic artery'/de) AND ('infusion'/de OR 'infusion pump'/de OR 'continuous infusion'/de OR 'cancer chemotherapy'/de OR 'liver metastasis'/de/dm_dt)) OR 'intraarterial drug administration'/de OR 'artery catheterization'/de OR (((arter* OR transarter* OR endoarter* OR intraarter* OR intrahepatic*) NEAR/6 (infusion* OR chemotherap* OR floxuridin* OR fluorodeoxyuridin* OR fluorouracil* OR pump* OR therap* OR catheter* OR inject* OR cannul* OR implant* OR port OR ports)) OR HAI OR HAIP):ab,ti,kw) AND ('colorectal liver metastasis'/exp OR (('liver metastasis'/de OR ('liver tumor'/de AND metastasis/de)) AND ('rectum cancer'/exp OR 'colon cancer'/exp OR 'colorectal tumor'/exp)) OR (((colorectal OR colon* OR rectum OR rectal OR CRC OR anorect*) AND (liver OR hepatic*) NEAR/6 metasta*)):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

Medline Ovid

((("hepatic artery"/) AND ("Infusions, Parenteral"/ OR "Infusion Pumps"/ OR "Chemotherapy, Cancer, Regional Perfusion"/)) OR "Infusions, Intra-Arterial"/ OR "Injections, Intra-Arterial"/ OR (((arter* OR transarter* OR endoarter* OR intraarter* OR intrahepatic*) ADJ6 (infusion* OR chemotherap* OR floxuridin* OR fluorodeoxyuridin* OR fluorouracil* OR pump* OR therap* OR catheter* OR inject* OR cannul* OR implant* OR port OR ports)) OR HAI OR HAIP).ab,ti,kf.) AND ((((("Liver Neoplasms"/ AND "Neoplasm Metastasis"/)) AND (exp "Colorectal Neoplasms"/)) OR (((colorectal OR colon* OR rectum OR rectal OR CRC OR anorect*) AND (liver OR hepatic*) ADJ6 metasta*)).ab,ti,kf.) NOT (exp animals/ NOT humans/) NOT (news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane

((((arter* OR transarter* OR endoarter* OR intraarter* OR intrahepatic*) NEAR/6 (infusion* OR chemotherap* OR floxuridin* OR fluorodeoxyuridin* OR fluorouracil* OR pump* OR therap* OR catheter* OR inject* OR cannul* OR implant* OR port OR ports)) OR HAI OR HAIP):ab,ti,kw) AND ((((colorectal OR colon* OR rectum OR rectal OR CRC OR anorect*) AND (liver OR hepatic*) NEAR/6 metasta*)):ab,ti,kw)

Web of science

TS=(((((arter* OR transarter* OR endoarter* OR intraarter* OR intrahepatic*) NEAR/5 (infusion* OR chemotherap* OR floxuridin* OR fluorodeoxyuridin* OR fluorouracil* OR pump* OR therap* OR catheter* OR inject* OR cannul* OR implant* OR port OR ports)) OR HAI OR HAIP)) AND ((((colorectal OR colon* OR rectum OR rectal OR CRC OR anorect*) AND (liver OR hepatic*) NEAR/5 metasta*)))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(english)

Google scholar

First 200:

"arterial|intraarterial|intrahepatic
infusion|chemotherapy|floxuridine|fluorodeoxyuridine|pump"
colorectal|colon|rectum|rectal|CRC "liver|hepatic metastases|metastasis"

'arterial|intraarterial|intrahepatic
infusion|chemotherapy|floxuridine|fluorodeoxyuridine|pump'
colorectal|colon|rectum|rectal|CRC 'liver|hepatic metastases|metastasis'

First 100:

allintitle:"arterial|intraarterial|intrahepatic infusion|chemotherapy|floxuridine|fluorodeoxyuridine|pump" "liver|hepatic metastases|metastasis"

allintitle:'arterial|intraarterial|intrahepatic infusion|chemotherapy|floxuridine|fluorodeoxyuridine|pump' 'liver|hepatic metastases|metastasis

Supplementary files. Quality assessment of non-randomized studies (Ottawa Newcastle)

	Study	Ambiru	Kusunoki	Moroz	Onaitis	Bolton	Goéré	Gr. Koerkamp
Selection	1) Representativeness of the exposed cohort	a) Truly representative of the average population	a) Truly representative of the average population	a) Truly representative of the average population	a) Truly representative of the average population	b) Somewhat representative of the average population	b) Somewhat representative of the average population	a) Truly representative of the average population
	Score	1	1	1	1	0	0	1
	2) Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort	a) Drawn from the same community as the exposed cohort	a) Drawn from the same community as the exposed cohort	a) Drawn from the same community as the exposed cohort	a) Drawn from the same community as the exposed cohort	a) Drawn from the same community as the exposed cohort	a) Drawn from the same community as the exposed cohort
	Score	1	0	1	1	1	1	1
	3) Ascertainment of Exposure	a) Secure record	a) Secure record	a) Secure record	a) Secure record	a) Secure record	a) Secure record	a) Secure record
	Score	1	1	1	1	1	1	1
	4) Demonstration that outcome of interest was not present at start of study	a) Yes	a) Yes	a) Yes	a) Yes	a) Yes	a) Yes	a) Yes
	Score	1	1	1	1	1	1	1

(Cont.)	**Study**	Ambiru	Kusunoki	Moroz	Onaitis	Bolton	Goéré	Gr. Koerkamp
Comparability	1) Comparability of cohorts on the basis of the design or analysis	c) No multivariable analysis	c) No multivariable analysis	b) Study controls for additional factor	c) No multivariable analysis	c) No multivariable analysis	b) Study controls for additional factor	b) Study controls for additional factor
	Score	0	0	2	0	0	2	2
Outcome	1) Assessment of outcome	b) Record linkage	b) Record linkage	b) Record linkage	b) Record linkage	b) Record linkage	b) Record linkage	b) Record linkage
	Score	1	1	1	1	1	1	1
	2) was follow-up long enough for outcomes to occur	b) No	a) Yes	b) No	b) No	a) Yes	a) Yes	a) Yes
	Score	0	1	0	0	1	1	1
	3) Adequacy of follow-up of cohorts	a) Complete follow up - all subjects accounted for	a) Complete follow up - all subjects accounted for	a) Complete follow up - all subjects accounted for	a) Complete follow up - all subjects accounted for	a) Complete follow up - all subjects accounted for	a) Complete follow up - all subjects accounted for	a) Complete follow up - all subjects accounted for
	Score	1	1	1	1	1	1	1
Total score	**Selection (tot. 4)**	**4**	**3**	**4**	**4**	**3**	**3**	**4**
	Comparability (tot. 2)	**0**	**0**	**2**	**0**	**0**	**2**	**2**
	Outcome (tot. 3)	**2**	**3**	**2**	**2**	**3**	**3**	**3**

Supplementary files. Quality assessment of randomized studies (RoB 2)

Domain 1: Risk of bias arising from the randomization process	Wagman	Lorenz	Rudroff	Tono	KemenyM	KemenyN	Kusano 2017	Kusano 2018
1.1 Was the allocation sequence random?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No	No	No	No	No	No	No	No
Risk-of-bias judgement	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)								
2.1. Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No	No	No	No	No	No	No	No
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA	NA	NA	NA	NA	NA	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA	NA	NA	NA	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No	NA	NA	NA	NA	NA	NA	NA
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No	Yes	No	NA	NA	NA	No	No
Risk-of-bias judgement	**Low**	**High**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Wagman	Lorenz	Rudroff	Tono	KemenyM	KemenyN	Kusano 2017	Kusano 2018
2.1. Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	No	Yes	No	No	PY	No	PY	PY
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	No	Yes	No	NA	No	No	PY	PY
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	No	NA	NA	No	NA	No	No
Risk-of-bias judgement	Low	High	Low	Low	Low	Low	Low	Low
Domain 3: Missing outcome data								
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	No	No	Yes	Yes	Yes	Yes	Yes	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Yes	Yes	No	No	No	No	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Yes	Yes	NA	NA	NA	NA	NA	NA
Risk-of-bias judgement	**High**	**high**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

Domain 4: Risk of bias in measurement of the outcome	Wagman	Lorenz	Rudroff	Tono	KemenyM	KemenyN	Kusano 2017	Kusano 2018
4.1 Was the method of measuring the outcome inappropriate?	No	Yes	Yes	No	Yes	Yes	Yes	Yes
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No	No	No	No	No	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No	No	No	No	No	No	No	No
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No	No	No	No	No	No	No	No
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No	No	No	No	No	No	No
Risk-of-bias judgement	**Low**	**Some**	**Some**	**Low**	**Low**	**Low**	**Low**	**Low**
Domain 5: Risk of bias in selection of the reported result								
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before outcome data were available for analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...								
5.2. ... multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	PY	Yes	Yes	Yes	no	No	No	No
5.3 ... multiple eligible analyses of the data?	No	No	No	no	no	No	No	No
Risk-of-bias judgement	Some	Some	Some	Some	Low	no	no	no
Overall risk of bias	**High**	**High**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

Chapter 4

Recurrence patterns after resection of colorectal liver metastasis are modified by perioperative systemic chemotherapy

F.E. Buisman, B. Galjart, E.P. van der Stok, V.P. Balachandran, T. Boerner, J.A. Drebin, D.J. Grünhagen, W.R. Jarnagin, T.P. Kingham, C. Verhoef, M.I. D'Angelica, B. Groot Koerkamp

World Journal of Surgery 2020; 44(3):268-886

Abstract

Background

This study investigated the impact of perioperative systemic chemotherapy on the recurrence rate and pattern following resection of colorectal liver metastases.

Methods

A retrospective cohort study was conducted in two centers. Rates and patterns of recurrence and overall survival (OS) were compared between patients treated with and without perioperative systemic chemotherapy. The clinical risk score (CRS) was used to stratify patients in low-risk (CRS 0-2) and high-risk (CRS 3-5) of recurrence.

Results

A total of 2020 patients were included, of whom 1442 (71%) received perioperative systemic chemotherapy. The median follow-up was 88 months, and 1289 patients (64%) developed a recurrence. The recurrence pattern was independent of chemotherapy in low-risk patients: intrahepatic recurrences (30% vs 30%, $p = 0.97$) and extrahepatic recurrences (38% vs. 39%, $p = 0.52$). In high-risk patients, no difference in intrahepatic recurrences was found (48% vs. 50%, $p = 0.59$). However, a lower rate of extrahepatic recurrences (43% vs. 55%, $p = 0.007$) was observed with perioperative systemic chemotherapy, mainly due to a reduction in pulmonary recurrences (25% vs 35%, $p = 0.007$). In competing risk analysis, the cumulative incidence of extrahepatic recurrence was significantly lower with perioperative systemic chemotherapy in high-risk patients only (5-year cumulative incidence 44% vs 59%, $p < 0.001$). Perioperative chemotherapy was associated with improved OS in high-risk patients (adjusted HR 0.73, 95% CI 0.57-0.94, $p = 0.02$), but not in low-risk patients (adjusted HR 0.99, 95% CI 0.82-1.19, $p = 0.90$).

Conclusions

Perioperative systemic chemotherapy had no association with intrahepatic recurrence, but was associated with fewer pulmonary recurrences and superior OS in high-risk patients only.

Introduction

After surgery for colorectal liver metastasis (CRLM), up to 70% of patients develop recurrent disease. Recurrences occur mostly within the first 2 years after resection.[1] The 5-year survival probability is about 50% after curative-intent resection of CRLM.[2]

Perioperative systemic chemotherapy was found to improve progression-free survival (PFS), but not overall survival (OS) in a randomized controlled trial.[2] In some countries (e.g., USA), perioperative systemic chemotherapy is the standard of care in patients with resectable CRLM; in other countries (e.g., the Netherlands) it is not. Some studies suggested that the truth lies in the middle. They found that only patients with high-risk oncological features have superior OS with perioperative systemic chemotherapy.[3-5] In the above mentioned randomized trial, mainly patients with low-risk oncological features were included.[2] The clinical risk score (CRS) stratifies patients in subgroups of low-risk and high-risk of recurrence and OS.[6] The CRS is the sum of five poor prognostic factors, assigning one point to each factor if present: positive nodal status of primary tumor, disease-free interval between resection of primary and diagnosis of CRLM less than 1 year, more than one CRLM, size of largest CRLM exceeding 5 cm, and preoperative serum carcinoembryonic antigen (CEA) level above 200 µg/L. Patients can be stratified into low-risk (0-2 points) and high-risk (3-5 points) of recurrence.[6]

Perioperative systemic chemotherapy may avoid or postpone intrahepatic and/or extrahepatic recurrence after resection of CRLM. The aim of this study is to investigate the impact of perioperative systemic chemotherapy on the recurrence rate and pattern in low- and high-risk patients after resection of CRLM.

Materials and method

Patients

Patients who underwent surgical treatment for CRLM between 1991 and 2012 at the Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA), and between 2000 and 2016 at the Erasmus MC Cancer Institute (Rotterdam, the Netherlands), were evaluated for inclusion. At MSKCC, perioperative systemic chemotherapy was typically administered in the induction, neoadjuvant, and/or adjuvant setting. At Erasmus MC, patients received perioperative systemic chemotherapy almost exclusively as induction chemotherapy for initially (borderline) unresectable CRLM, according to the Dutch national guidelines. This study was conducted according to the STROBE guidelines.

Inclusion and exclusion criteria

Patients were excluded from analysis for the following reasons: administration of perioperative hepatic arterial infusion pump (HAIP) chemotherapy, extrahepatic disease

(EHD) diagnosed before or at the time of CRLM resection, no complete liver resection, no resection of the primary tumor, lost to follow-up, and ablative procedures without CRLM resection. Patients treated with a combined resection and ablation (radio frequency ablation (RFA) or microwave ablation (MWA)) were eligible. Patients that could not be classified in low-risk or high-risk due to missing values were excluded from further analyses.

Definitions

Clinicopathological data were retrieved from two prospectively maintained databases. Data on patient and tumor characteristics, surgical outcome, recurrence of disease, and survival were gathered. Only the site(s) of initial recurrence were available. Perioperative systemic chemotherapy was defined as any systemic chemotherapy within 3 months of resection. EHD was defined as the presence of disease outside the liver (other than the primary CRC) prior to or at surgery. Primary tumors were classified as right-sided if localized proximal to the splenic flexure, left-sided tumors if localized at or distal to the splenic flexure, or rectal tumors. The total number of CRLM was calculated by the total number of lesions at the pathology report combined with the total number of lesions ablated. The size of largest tumor was derived from the pathology report. Patients were stratified into low-risk (CRS 0-2) and high-risk (CRS 3-5).[6] Recurrences were classified into intrahepatic or extrahepatic. Since patients could have an initial recurrence in more than one organ, the sum of intrahepatic and extrahepatic recurrence exceeds the total recurrence rate.

Statistical analysis

Baseline characteristics were compared using the Chi-square test for categorical variables, and the Mann-Whitney U-test for continuous variables. Median follow-up time was calculated using the reversed Kaplan-Meier method. OS was defined from the date of resection of CRLM until the date of death or last follow-up. The Kaplan-Meier method was used to calculate OS. Groups were compared using the log-rank test. Uni- and multivariable Cox regression analyses for OS were performed, and results were presented as hazard ratios (HR) with corresponding 95% confidence intervals (CIs). Cumulative incidence functions (CIF) for patients treated with and without perioperative systemic chemotherapy were estimated using competing risk methods and compared over the entire follow-up time using Gray's test.[7] A CIF estimates the probability of an event up to a follow-up time point *t*. The cumulative incidence was adjusted by the occurrence of the competing events. Patients developing a competing event (i.e., initial recurrence at a specific location other than the location of interest or dying before they have developed a recurrence) were no longer at risk for the event of interest. A p-value smaller than 0.05 was considered statistically significant. Analyses were performed using SPSS (IBM Corp, version 24, Armonk, NY) and RStudio (RStudio, version 1.0.153, Boston, MA).

Follow-up

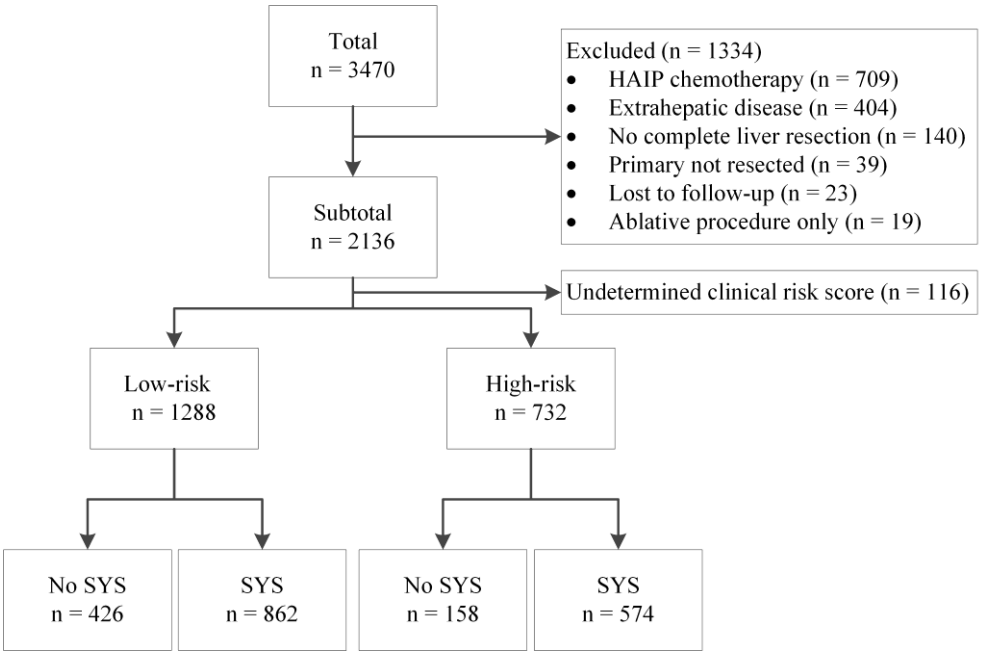
During follow-up at MSKCC, serum CEA measurements and radiological imaging (abdominal and thoracic CT-scan) were performed every 3-6 months for the first three years

and yearly thereafter. At Erasmus MC follow-up was similar to radiological imaging every 3-6 months for the first 2 years, and yearly thereafter until 5 years.

Results

A total of 3470 patients were evaluated for inclusion (Figure 1). Approximately 38% (n = 1334) of the patients were excluded, primarily due to perioperative HAIP chemotherapy (53.1%, n = 709) and the presence of EHD (30.3%, n = 404). The remaining 2020 patients were included for analysis, of whom 1442 patients (71.4%) received perioperative systemic chemotherapy. Most patients were treated at MSKCC (n = 1244, 61.6%) and the remainder at Erasmus MC (n = 776, 38.4%). At MSKCC 1102 (88.6%) patients received perioperative systemic chemotherapy compared to 334 (43.0%) patients at Erasmus MC ($p < 0.001$). Perioperative systemic chemotherapy was administered preoperatively in 568 patients (39.9%), postoperatively (i.e., adjuvant) in 404 patients (28.1%), and both pre- and postoperatively in 464 patients (32.3%). Most patients received either oxaliplatin- or irinotecan-based therapy (72.3%), and the remainder received 5-fluorouracil-based monotherapy, mostly in the era prior to oxaliplatin and irinotecan.

Figure 1. Study flowchart



Clinical risk score

Most patients were classified according to the CRS as low-risk (n = 1288, 63.7%), and about a third as high-risk (n = 732, 36.3%). A complete overview of the number of patients within each CRS class can be found in Supplementary Table 1. High-risk patients more often received perioperative systemic chemotherapy compared to low- risk patients (78.4% vs. 67.3%, $p < 0.001$). The baseline characteristics of low-risk and high-risk patients are stratified by whether they received perioperative systemic chemotherapy (Table 1). Low-risk patients treated with perioperative systemic chemotherapy were younger at the time of resection of the CRLM (median age 64.4 months vs. 67.0 months, $p < 0.001$), were more likely to have right-sided CRC (24.9% vs. 19.2%, $p = 0.01$), more often had a DFI of less than 12 months (50.3% vs. 41.1%, $p = 0.002$), more than 1 CRLM (33.8% vs. 27.0%, $p = 0.01$), or CRLM smaller than 5 cm (86.2% vs. 81.2%, $p = 0.02$). For high-risk patients, no statistically significant differences were found between patients treated with and without perioperative systemic chemotherapy.

Table 1. Baseline characteristics

	Low-risk				High-risk			
	All patients	**No SYS**	**SYS**	**P-value**	**All patients**	**No SYS**	**SYS**	**P-value**
	n (%)	*n (%)*	*n (%)*		*n (%)*	*n (%)*	*n (%)*	
Sample size	1288	426 (33.1)	862 (66.9)	-	732	158 (21.7)	574 (78.4)	-
Age (median, IQR)	65.5 (57.0-72.3)	67.0 (60.0-74.0)	64.4 (55.7-71.4)	<0.001	62.1 (53.0-70.0)	64.0 (58.0-72.0)	62.0 (51.6-69.4)	0.15
Gender				0.63				0.71
Male	794 (61.6)	267 (62.7)	527 (61.1)		448 (61.2)	99 (62.7)	349 (60.8)	
Female	494 (38.4)	159 (37.3)	335 (38.9)		284 (38.8)	59 (37.3)	225 (39.2)	
Primary tumor location				0.01				0.60
Right-sided	288 (23.0)	79 (19.2)	209 (24.9)		196 (27.3)	41 (26.5)	155 (27.5)	
Left-sided	559 (44.7)	180 (43.7)	379 (45.2)		327 (45.5)	67 (43.2)	260 (46.2)	
Rectum	404 (32.3)	153 (37.1)	251 (29.9)		195 (27.2)	47 (30.3)	148 (26.3)	
Missing	37				14			
Nodal status primary tumor				0.09				0.84
N0	751 (58.6)	262 (61.9)	489 (57.0)		77 (10.6)	16 (10.1)	61 (10.7)	
N+	530 (41.4)	161 (38.1)	369 (43.0)		652 (89.4)	142 (89.9)	510 (89.3)	
Missing	7				3			
Disease free interval				0.002				0.82
≤ 12 months	609 (47.3)	175 (41.1)	434 (50.3)		684 (93.4)	147 (93.0)	147 (93.0)	
> 12 months	679 (52.7)	251 (58.9)	428 (49.7)		48 (6.6)	11 (7.0)	11 (7.0)	
Number CRLM				0.01				0.59
≤ 1	882 (68.5)	311 (73.0)	571 (66.2)		80 (11.0)	19 (12.2)	61 (10.6)	
> 1	406 (31.5)	115 (27.0)	291 (33.8)		649 (89.0)	137 (87.8)	512 (89.4)	
Missing					3			
Size largest tumor				0.02				0.33
≤ 5cm	1079 (84.6)	337 (81.2)	742 (86.2)		462 (63.7)	104 (67.1)	358 (62.8)	
> 5cm	197 (15.4)	78 (18.8)	119 (13.8)		263 (36.3)	51 (32.9)	212 (37.2)	
Missing	12				7			

(Continued)	Low-risk				High-risk			
	All patients	**No SYS**	**SYS**	**P-value**	**All patients**	**No SYS**	**SYS**	**P-value**
CEA				0.27				0.78
≤ 200 µg/L	1204 (97.3)	400 (96.6)	804 (97.7)		531 (78.9)	118 (79.7)	413 (78.7)	
> 200 µg/L	33 (2.7)	14 (3.4)	19 (2.3)		142 (21.1)	30 (20.3)	112 (21.3)	
Missing	51				59			
Resection margin involved				0.66				0.65
Yes	109 (8.5)	38 (9.0)	71 (8.3)		115 (15.7)	23 (14.6)	92 (16.1)	
No	1166 (91.5)	382 (91.0)	784 (91.7)		616 (83.3)	135 (85.4)	481 (83.9)	
Missing	13				1			
Tumor ablation at time of resection				0.09				0.90
Yes	78 (6.1)	19 (4.5)	59 (6.8)		165 (22.5)	35 (22.2)	130 (22.6)	
No	1210 (93.9)	407 (95.5)	803 (93.2)		567 (77.5)	123 (77.8)	444 (77.4)	

Abbreviations: CEA: carcinoembryonic antigen, CRLM: colorectal liver metastasis, SYS: systemic chemotherapy

Recurrence rates

The median follow-up for survivors for all patients was 88 months (interquartile range (IQR) 50-129 months). In total 1154 patients (57.1%) died during follow-up. During follow-up 1289 patients (63.8%) developed a recurrence after resection of CRLM. A total of 741 low-risk patients (57.5%) developed a recurrence compared to 548 high-risk patients (74.9%, $p < 0.001$). The overall recurrence rate with and without perioperative systemic chemotherapy was similar in both low-risk (57% vs. 58%, $p = 0.73$) and high-risk patients (74% vs. 77%, $p = 0.44$).

Recurrence pattern and OS in low-risk patients

Organ-specific recurrence patterns are presented in Table 2. Among low-risk patients (Figure 2a and 2b), no difference in initial intrahepatic recurrence rate was found between both treatment groups (30% vs. 30%, $p = 0.97$). Similar, no difference was found in the rate of extrahepatic recurrence (38% vs. 39%, $p = 0.52$) and of pulmonary recurrence (23% vs. 27%, $p = 0.21$). Subdividing of low-risk patients in CRS 0, 1, and 2 did not change the results (Supplementary Table 2).

Table 2. Recurrences by location

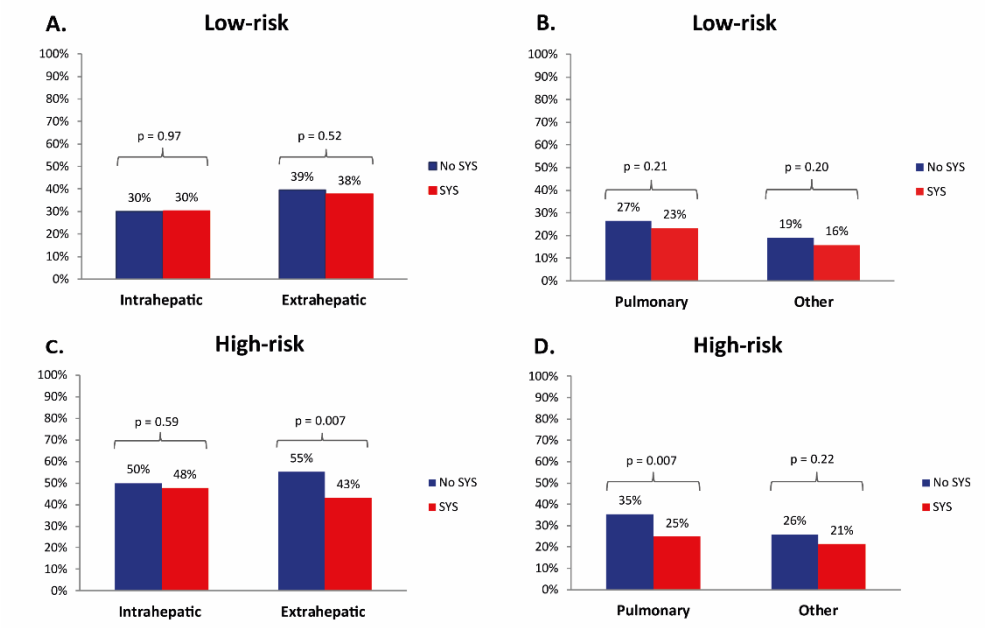
	Low-risk			High-risk		
Location	**No SYS**	**SYS**	**P-value**	**No SYS**	**SYS**	**P-value**
	n (%)	*n (%)*		*n (%)*	*n (%)*	
Intrahepatic	128 (30.0)	260 (30.2)	0.97	79 (50.0)	273 (47.6)	0.59
Pulmonary	113 (26.5)	201 (23.3)	0.21	56 (35.4)	142 (24.7)	0.007
Distant lymph nodes	28 (6.6)	47 (5.5)	0.42	18 (11.4)	49 (8.5)	0.27
Peritoneal	7 (1.6)	18 (2.1)	0.59	10 (6.3)	20 (3.5)	0.11
Local recurrence	12 (2.8)	35 (4.1)	0.26	5 (3.2)	22 (3.8)	0.69
Bone	6 (1.4)	11 (1.3)	0.85	4 (2.5)	15 (2.6)	0.95
Other	19 (4.5)	41 (4.8)	0.81	8 (5.1)	34 (5.9)	0.68

Abbreviations: SYS: systemic chemotherapy

These results were confirmed in competing risk analysis (Figure 3a, b), showing no difference in the incidence of intrahepatic recurrence ($p = 0.68$; 5-year cumulative incidence 31% vs. 32%), and no difference in the incidence of extrahepatic recurrence ($p = 0.08$; 5-year cumulative incidence 39% vs. 42%). Subdividing of low-risk patients in CRS 0, 1, and 2 did not change the results (Supplementary Figure 1).

In terms of survival (Figure 4a), no benefit on median OS for low-risk patients treated with perioperative systemic chemotherapy was found (66 months vs. 63 months, $p = 0.51$). In multivariable analysis for OS in low-risk patients, perioperative systemic chemotherapy was not an independent prognostic factor (adjusted HR 0.99, 95% CI 0.82-1.19, $p = 0.90$, Table 3a).

Figure 2. Recurrence patterns stratified by CRS



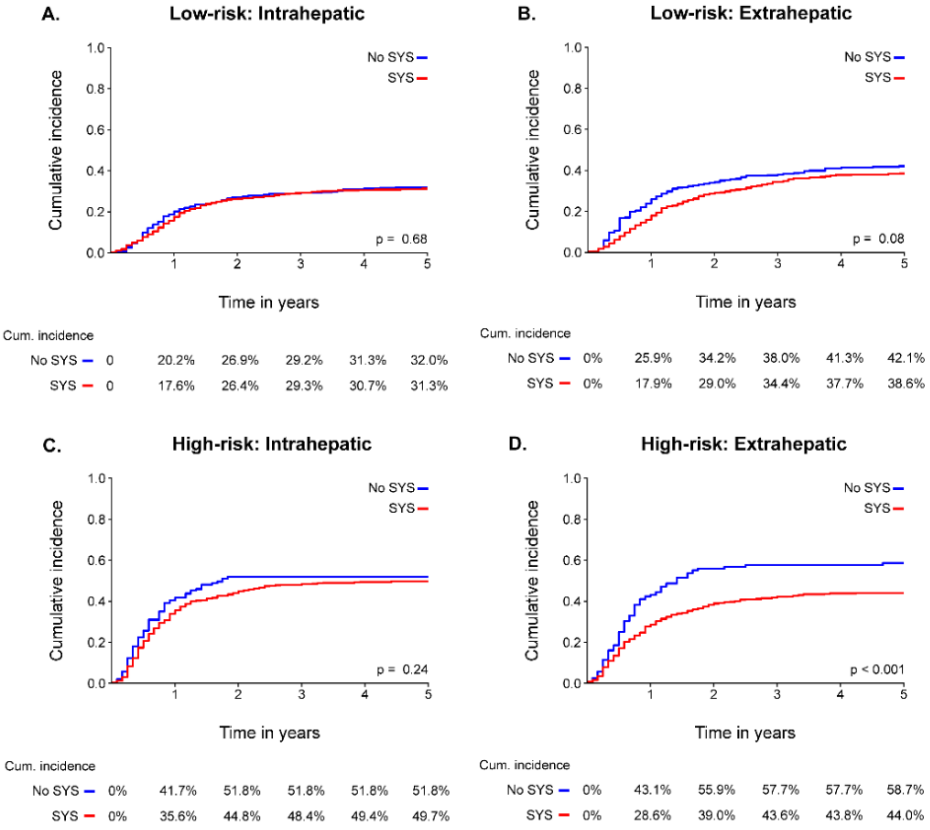
Only initial recurrences are counted. Patients can have multiple initial recurrence sites, for example, intrahepatic and pulmonary.

Table 3a. Multivariable Cox regression analysis for overall survival of low-risk patients

	Univariable analysis			Multivariable analysis		
Covariate	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at resection	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	<0.001
Right-sided tumor	1.15	0.94-1.41	0.17	1.10	0.89-1.36	0.40
Node positive primary tumor	1.18	1.02-1.38	0.03	1.40	1.19-1.65	<0.001
Disease-free interval (cont.)	1.00	1.00-1.01	0.26	0.99	0.99-1.00	0.01
Number CRLM (cont.)	1.06	1.01-1.12	0.02	1.08	1.07-1.1	0.005
Diameter CRLM (cont.)	1.09	1.07-1.12	<0.001	1.10	1.07-1.13	<0.001
Preoperative CEA (cont.)	1.00	1.00-1.00	0.007	1.00	1.00-1.00	0.03
Irradical resection (R1)	1.67	1.32-2.13	<0.001	1.58	1.22-2.03	<0.001
Additional ablation	1.17	0.82-1.66	0.39	1.34	0.90-2.01	0.15
Year of surgery	0.98	0.97-1.00	0.008	0.99	0.98-1.01	0.22
Perioperative SYS	0.95	0.81-1.11	0.51	0.99	0.82-1.19	0.90

Abbreviations: CEA: carcinoembryonic antigen, CI: confidence interval, CRLM: colorectal liver metastases, HR: hazard ratio, SYS: systemic chemotherapy

Figure 3. Cumulative incidence function for location specific recurrence stratified by CRS



Recurrence pattern and OS in high-risk patients

An overview of recurrence patterns in high-risk patients is presented in Table 2. Among high-risk patients (Figure 2c, 2d), no difference in initial intrahepatic recurrence rate was found between both treatment groups (48% vs. 50%, p = 0.59). A lower rate of extrahepatic recurrence was found after treatment with perioperative systemic chemotherapy (43% vs. 55%, p = 0.007). This was largely explained by a difference in pulmonary recurrence with perioperative systemic chemotherapy (25% vs. 35%, p = 0.007). Subdividing of low-risk patients in CRS 3, 4, and 5 demonstrated that the effect was primarily due to a difference in patients with a CRS of 3, however number of patients with a CRS of 4 or 5 is limited (Supplementary Table 2).

These results were confirmed in competing risk analysis (Figure 3c, d), showing no difference in the incidence of intrahepatic recurrence (p = 0.24; 5-year cumulative incidence 50% vs. 52%), but a significant reduction of extrahepatic recurrence after perioperative systemic chemotherapy (p < 0.001; 5-year cumulative incidence 44% vs. 59%). Subdividing of low-risk patients in CRS 3, 4, and 5 demonstrated that the difference in cumulative

difference was primarily due to a difference in patients with a CRS of 3 (Supplementary Figure 2).

Moreover, high-risk patients treated with perioperative systemic chemotherapy (Figure 4b) had a superior OS compared to patients that were not treated with perioperative systemic chemotherapy (median OS 43 months vs. 33 months, p = 0.02). Finally, perioperative systemic chemotherapy was an independent prognostic factor (adjusted HR 0.73, 95%CI 0.57-0.94, p = 0.02) in multivariable for OS (Table 3b).

Figure 4. Kaplan-Meier analysis for overall survival stratified by CRS

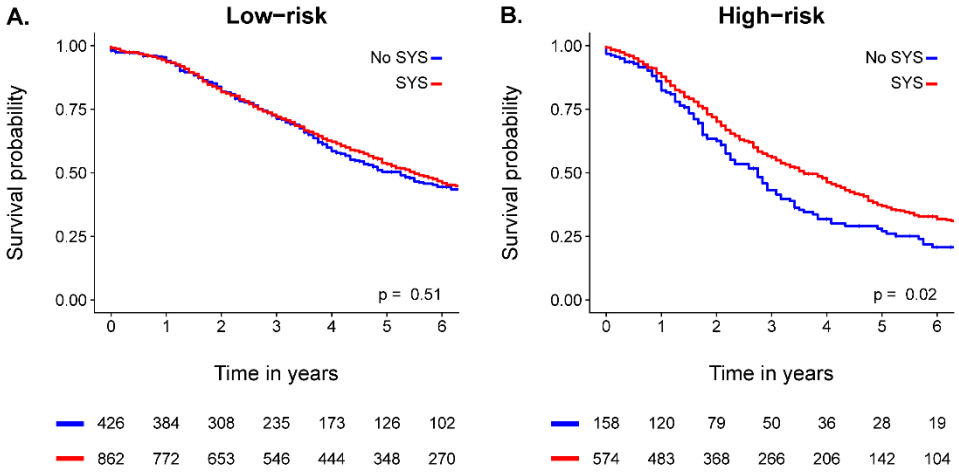


Table 3b. Multivariable Cox regression analysis for overall survival of high-risk patients

	Univariable analysis			Multivariable analysis		
Covariate	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at resection	1.02	1.01-1.02	0.001	1.01	1.00-1.02	0.005
Right-sided tumor	1.46	1.13-1.87	0.004	1.32	1.00-1.74	0.05
Node positive primary tumor	1.04	0.77-1.39	0.82	1.36	0.97-1.90	0.08
Disease-free interval (cont.)	1.01	1.00-1.02	0.009	1.00	0.99-1.01	0.97
Number CRLM (cont.)	1.08	1.05-1.10	<0.001	1.06	1.04-1.09	<0.001
Diameter CRLM (cont.)	1.04	1.02-1.07	<0.001	1.04	1.01-1.07	0.006
Preoperative CEA (cont.)	1.00	1.00-1.00	0.75	1.00	1.00-1.00	0.17
Irradical resection (R1)	1.38	1.09-1.76	0.008	1.33	1.02-1.75	0.04
Additional ablation	1.04	0.82-1.32	0.74	1.35	1.00-1.81	0.05
Year of surgery	0.97	0.96-0.98	0.008	0.97	0.95-0.99	0.001
Perioperative SYS	0.76	0.61-0.95	0.02	0.73	0.57-0.94	0.02

Abbreviations: CEA: carcinoembryonic antigen, CI: confidence interval, CRLM: colorectal liver metastases, HR: hazard ratio, SYS: systemic chemotherapy

Discussion

We found a significant decrease in extrahepatic recurrences (43% vs. 55%, p = 0.007) in high-risk patients treated with perioperative systemic chemotherapy. This was confirmed in a competing risk analysis; 5-year cumulative incidence of extrahepatic recurrence was 44% with perioperative systemic chemotherapy vs. 59% without (p < 0.001). This decrease in extrahepatic recurrences could largely be attributed to a decrease in pulmonary recurrences (25% vs. 35%, p = 0.007). No difference in intrahepatic recurrence rate was found. Moreover, low-risk patients had similar recurrence rates and patterns with and without perioperative systemic chemotherapy.

In the present study, 1289 patients (64%) developed a recurrence after resection of CRLM. Approximately equal rates of recurrence were found in a previous study of 1669 patients after curative resection of CRLM. In that study, after a median follow-up of 30 months, 947 (57%) of patients developed a recurrence.[8] This study reported intrahepatic recurrences in 36% of the patients and similarly extrahepatic recurrences in 36% of the patients.

Another large study evaluating 2320 patients after resection of CRLM reported a recurrence rate of 47% after a median follow-up of only 27 months.[9] The proportion of patients with an intrahepatic recurrence was 32%, compared to 25% for extrahepatic recurrence. Both studies underestimated the recurrence rate because of a much shorter length of follow-up and a smaller proportion of high-risk patients.

Based on the results of previous studies, the role of perioperative systemic chemotherapy in patients with resectable CRLM is still debated.[2, 10, 11] No significant OS benefit was found in

a large randomized trial that evaluated the effectiveness of perioperative FOLFOX in patients with resectable CRLM (EORTC 40983).[2] Although OS was not the primary endpoint of the study, OS curves were overlapping, even after long-term follow-up.[12] Importantly, in the EORTC 40983 trial most patients had low-risk disease. Several non-randomized studies evaluated whether high-risk patients had superior OS with perioperative systemic chemotherapy.[3, 4] In the first study, a superior OS was found for high-risk patients treated with neoadjuvant chemotherapy (adjusted HR 0.57, 95% CI 0.39-0.84, p = 0.004).[3] A second study found similar results for adjuvant systemic chemotherapy (HR 0.40, 95% CI 0.23-0.70, p = 0.001).[4] The superior OS of perioperative systemic chemotherapy in high-risk patients was confirmed in the present much larger study. Moreover, we found that the superior OS could be explained by a reduction in pulmonary recurrences, without an impact on intrahepatic recurrences. Pulmonary recurrences were less common after perioperative systemic chemotherapy in high-risk patients (25% vs. 35%, p = 0.007). It appears that perioperative systemic chemotherapy can avoid the appearance of pulmonary recurrences with an absolute risk reduction of 10%. Moreover, competing risk analyses demonstrated that perioperative systemic chemotherapy can also avoid or postpone pulmonary recurrence in high-risk patients. This could explain the superior OS found in this subgroup. Subdividing CRS groups from 0 to 5 demonstrated that the effect found in high-risk patients is primarily a result of a difference found in patients with a CRS of 3; however, number of patients with a CRS of 4 and 5 is low, limiting interpretation of the results in these specific subgroups.

No such effect of perioperative systemic chemotherapy was found in low-risk patients, or for intrahepatic recurrence. In low-risk patients, both previous studies found similar OS with and without systemic chemotherapy.[3, 4] The present study confirmed these findings, and found no difference in OS when comparing low-risk patients with and without perioperative systemic chemotherapy. Moreover, we found that perioperative systemic chemotherapy did not improve OS because, possibly since no association on the recurrence rate and pattern in these low-risk patients (in contrast to high-risk patients) could be demonstrated (Figure 2a-b).

The retrospective nature of this study contributed to several limitations. The administration of chemotherapy was not at random, at MSKCC most patients received perioperative chemotherapy (88.6%) compared to a minority of patients at Erasmus MC (43.0%). The types and duration of chemotherapy regimens varied across centers and in time. However, most patients (72.3%) received oxaliplatin- or irinotecan-based regimens. Furthermore, follow-up differed between the two centers, which could have biased recurrence intervals. Moreover, baseline tumor characteristics between patients treated with and without perioperative systemic chemotherapy varied considerably in low-risk patients. Stratification of patients in low-risk and high-risk reduced bias, but residual differences in low-risk patients remained. However, for OS these differences were addressed in multivariable analysis. Secondly, the CRS does not consider new biomarkers such as the genetic alterations (e.g., in RAS and BRAF) or histopathological growth patterns.[13-17] A previous study demonstrated that KRAS codon 13 mutations were associated with extrahepatic recurrence free survival (HR 2.27, 95% CI 1.29-3.97, p = 0.004) and lung recurrence free survival (HR 2.32, 95% CI 1.12-

4.78).[16] Recently, a new clinical risk score (GAME score) was developed, which combines clinicopathological and biological indicators (such as RAS mutation status).[18] A significant improvement of the Harrell's C-index was found for the GAME score compared to the original CRS by Fong (0.65 vs. 0.58, p = 0.008).[18] Mutational status was not available for our cohort unfortunately. Until mutational status will be generally available, the CRS will remain a practical classification method to determine the risk of recurrence.

Based on the present study and other smaller studies with similar findings, we recommend considering perioperative systemic chemotherapy in high-risk patients in countries (such as the Netherlands) that currently do not recommend any systemic chemotherapy after resection of CRLM. Secondly, we recommend considering withholding perioperative systemic chemotherapy in low-risk patients in countries (such as the USA) that currently recommend systemic chemotherapy after resection of CRLM for all patients.

In conclusion, we found that perioperative systemic chemotherapy had no association with intrahepatic recurrence, but was associated with fewer pulmonary recurrences and superior OS in high-risk patients only.

References

1. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
2. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-1215.
3. Ayez N, van der Stok EP, Grunhagen DJ, et al. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol* 2015; 41(7):859-67.
4. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.
5. Parks R, Gonen M, Kemeny N, et al. Adjuvant chemotherapy improves survival after resection of hepatic colorectal metastases: analysis of data from two continents. *J Am Coll Surg* 2007; 204(5):753-61; discussion 761-3.
6. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
7. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of Statistics* 1988; 16(3):114-1154.
8. De Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: An international multi-institutional analysis of 1669 patients. *Ann Surg* 2009; 250(3):440-447.
9. Hallet J, Sa Cunha A, Adam R, et al. Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg* 2016; 103(10):1366-76.
10. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; 15(6):601-11.
11. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; 26(30):4906-11.
12. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-15.
13. Frentzas S, Simoneau E, Bridgeman VL, et al. Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat Med* 2016; 22(11):1294-1302.

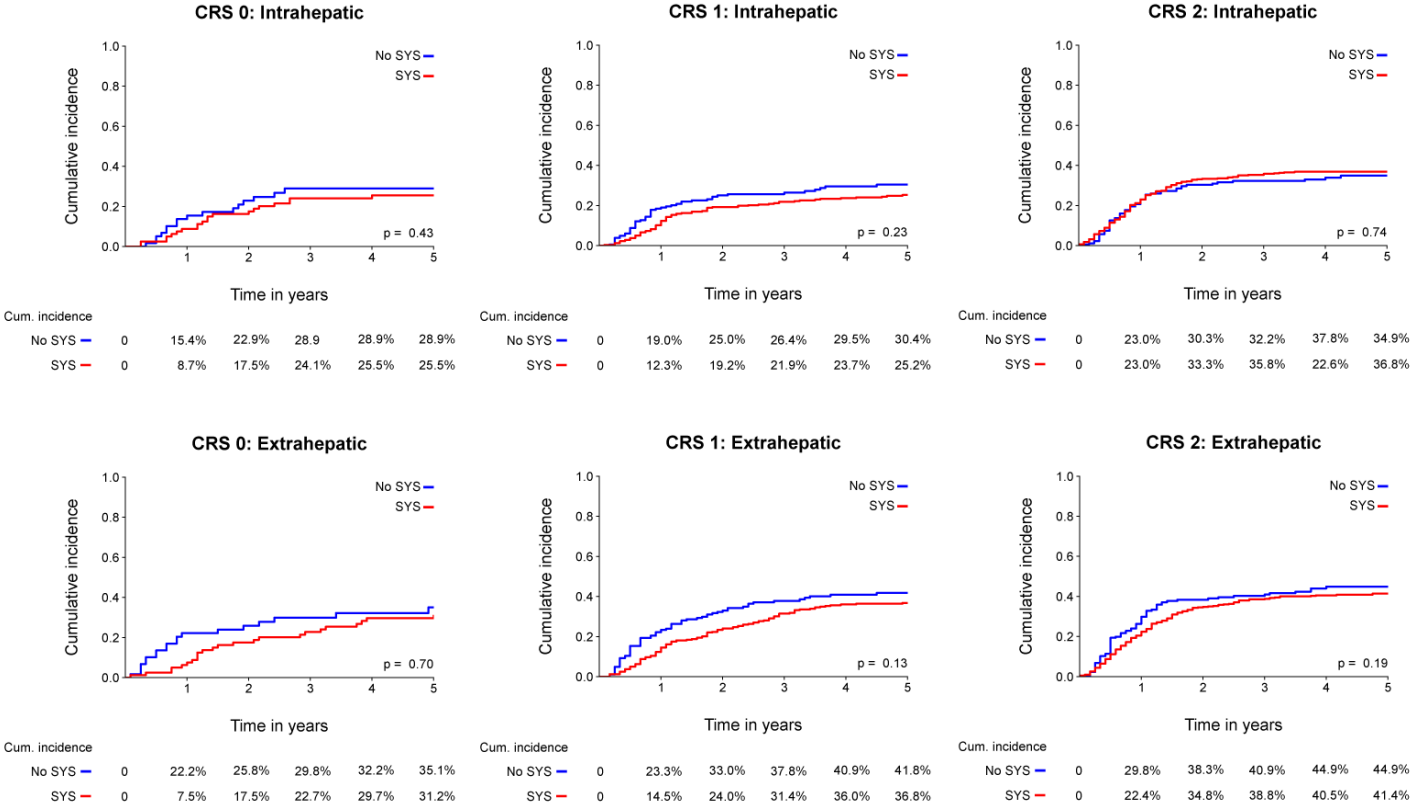
14. van Dam PJ, van der Stok EP, Teuwen LA, et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 2017; 117(10):1427-1441.
15. Margonis GA, Buettner S, Andreatos N, et al. Association of BRAF Mutations With Survival and Recurrence in Surgically Treated Patients With Metastatic Colorectal Liver Cancer. *JAMA Surg* 2018; 153(7):e180996.
16. Margonis GA, Kim Y, Sasaki K, et al. Codon 13 KRAS mutation predicts patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Cancer* 2016; 122(17):2698-707.
17. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg* 2013; 258(4):619-26; discussion 626-7.
18. Margonis GA, Sasaki K, Gholami S, et al. Genetic And Morphological Evaluation (GAME) score for patients with colorectal liver metastases. *Br J Surg* 2018.

Supplementary Table 1. Number of patients according to CRS class

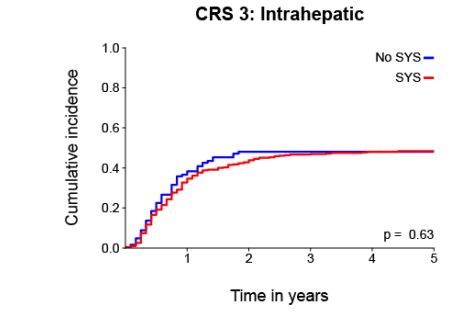
	All patients	No SYS	SYS	P-value
Clinical risk score				<0.001
0	141 (7.0%)	60 (10.3%)	81 (5.6%)	
1	518 (25.6%)	188 (32.2%)	330 (23.0%)	
2	629 (31.1%)	178 (30.5%)	451 (31.4%)	
3	570 (28.2%)	127 (21.7%)	443 (30.8%)	
4	131 (1.5%)	27 (4.6%)	104 (7.2%)	
5	31 (1.5%)	4 (0.7%)	27 (1.9%)	

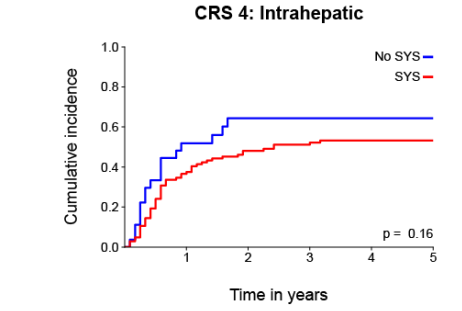
Abbreviations: SYS: systemic chemotherapy

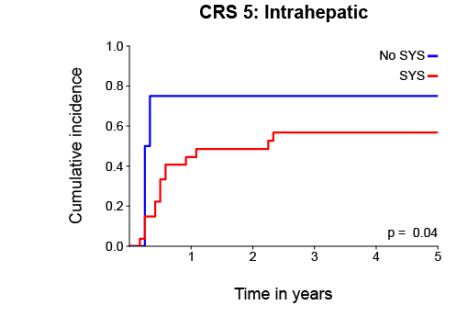
Supplementary Figure 1. Cumulative incidence function for location specific recurrence for CRS 0, 1 and 2

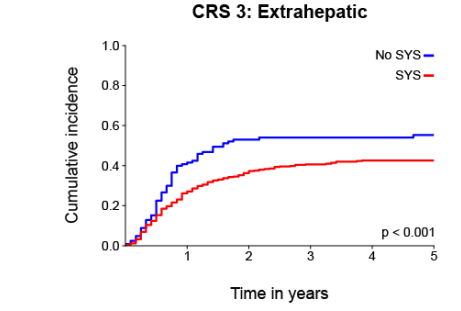


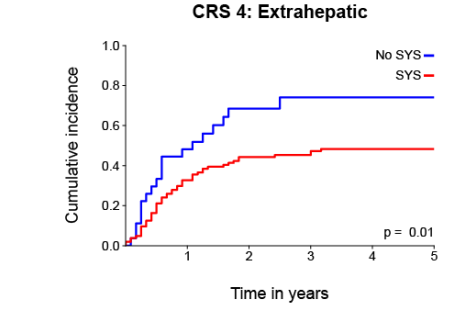
Supplementary Figure 2. Cumulative incidence function for location specific recurrence for CRS 3, 4 and 5

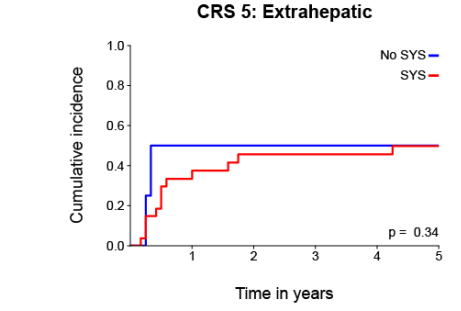












Chapter 5

The impact of hepatic arterial infusion pump chemotherapy on hepatic recurrences and survival in patients with resected colorectal liver metastases

F.E. Buisman, B. Galjart, E.P. van der Stok, N.E. Kemeny, V.P. Balachandran, T. Boerner, A. Cercek, D.J. Grünhagen, W.R. Jarnagin, T.P. Kingham, C. Verhoef, B. Groot Koerkamp, M.I. D'Angelica

HPB 2020; 22(9):1271-1279

Abstract

Background

The objective was to investigate the impact of adjuvant hepatic arterial infusion pump (HAIP) chemotherapy on the rates and patterns of recurrence and survival in patients with resected colorectal liver metastases (CRLM).

Methods

Recurrence rates, patterns, and survival were compared between patients treated with and without adjuvant HAIP using competing risk analyses.

Results

2128 patients were included, of which 601 patients (28.2%) received adjuvant HAIP and systemic chemotherapy (HAIP + SYS). The overall recurrence rate was similar with HAIP + SYS or SYS (63.5% vs. 64.2%, $p = 0.74$). The 5-year cumulative incidence of initial intrahepatic recurrences was lower with HAIP + SYS (22.9% vs. 38.4%, $p < 0.001$). The 5-year cumulative incidence of initial extrahepatic recurrences was higher with HAIP + SYS (48.5% vs. 40.3%, $p = 0.005$), because patients remained at risk for extrahepatic recurrence in the absence of intrahepatic recurrence, which was largely attributable to more pulmonary recurrences with HAIP + SYS (33.6% vs. 23.7%, $p < 0.001$). HAIP was an independent prognostic factor for DFS (adjusted HR 0.69, 95% CI 0.60-0.79, $p < 0.001$), and OS (adjusted HR 0.67, 95% CI 0.57-0.78, $p < 0.001$).

Conclusion

Adjuvant HAIP chemotherapy is associated with lower intrahepatic recurrence rates and better DFS and OS after resection of CRLM.

Introduction

Colorectal carcinoma (CRC) is the third leading cause of cancer-related death worldwide. Over one third of CRC patients develop colorectal liver metastases (CRLM).[1] Cure is still possible in patients with CRLM, however, recurrences after resection arise in approximately 70% of patients.[2] Both systemic chemotherapy and adjuvant hepatic arterial infusion pump (HAIP) chemotherapy aim to reduce recurrences after resection of CRLM.[3, 4]

HAIP chemotherapy involves continuous administration of intra-arterial of floxuridine into the liver using a subcutaneous pump.[5] The biological rationale behind HAIP chemotherapy is that the hepatic artery, rather than the portal vein is responsible for the blood supply of CRLM.[6, 7] Moreover, over 95% floxuridine (FUDR), which is an metabolite of 5-FU, is extracted by the liver during the first-pass. This allows for a 400-fold increase in hepatic exposure.[8, 9] The safety profile of HAIP chemotherapy has been evaluated in more than 500 patients.[10] Another recent study demonstrated the safety and feasibility of HAIP chemotherapy in two centers in the Netherlands.[11] Promising results on HAIP chemotherapy have been reported in previous studies.[4, 12-14] HAIP chemotherapy is routinely administered in combination with systemic chemotherapy. The use of adjuvant HAIP chemotherapy in patients with resectable CRLM is not widely implemented, although a randomized controlled trial (RCT) found superior survival.[12, 13] A more recent propensity score analysis of 2368 patients after resection of CRLM demonstrated a superior overall survival (OS) of almost two years in patients treated with HAIP.[4] This gain in survival is possibly effectuated by a reduction of intrahepatic recurrences, however the patterns of recurrence have not been studied thoroughly before. The aim of this study is to compare the rates and patterns of recurrence after resection of CRLM between patients who did and did not receive adjuvant HAIP chemotherapy.

Methods

The current study was approved by the institutional review board (IRB-number 16-533).

Patients

Patients who underwent surgical treatment for CRLM between 1991-2012 at the Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA), and between 2000-2016 at the Erasmus MC Cancer Institute (Rotterdam, the Netherlands), were evaluated for inclusion. Only patients who received preoperative and/or postoperative systemic chemotherapy (SYS) were included. HAIP chemotherapy with floxuridine was only administered at MKSCC and was offered to patients as part of a trial or at the discretion of their treating oncologists at MSKCC. A maximum of six cycles of adjuvant HAIP chemotherapy were administered starting from four weeks after surgery. Patients that were considered for HAIP chemotherapy but were not able to start due to various reasons remained in the HAIP + SYS chemotherapy

group. All patients that received HAIP chemotherapy received concurrent systemic chemotherapy. Most patients (over 75%) received oxaliplatin and/or irinotecan based systemic chemotherapy (e.g., FOLFOX or FOLFIRI regimes). About a quarter of these patients received additional bevacizumab (monoclonal antibody for vascular endothelial growth factor).

In- and exclusion criteria

Patients were excluded from analysis for the following reasons: no perioperative systemic chemotherapy, extrahepatic disease (EHD) before or at time of resection, preoperative HAIP chemotherapy, incomplete liver resection, no resection of the primary tumor, lost to follow-up, and ablative procedures without CRLM resection. Patients treated with a combined resection and ablation (radio frequency ablation (RFA) or microwave ablation (MWA)) procedure were included.

Definitions

Clinicopathological data were retrieved from two prospectively maintained databases. Data on patient and tumor characteristics, surgical outcome, recurrence of disease, and survival were retrieved. Only data on initial recurrences were analyzed. Perioperative systemic chemotherapy (SYS) was defined as any systemic chemotherapy within three months of resection. Extrahepatic disease was defined as presence of disease outside the liver prior to or at surgery. Primary tumors were classified as right-sided if localized proximal to the splenic flexure and left-sided tumors if localized at or distal to the splenic flexure, or rectal tumors. The total number of CRLM was calculated by the total number of lesions at the pathology report combined with the total number of lesions ablated. The size of largest tumor was derived from the pathology report. The clinical risk score (CRS) was used to stratify patients into low-risk (CRS 0-2) and high-risk (CRS 3-5) of recurrence of disease.[15] The CRS is the sum of five poor prognostic factors: node-positive CRC, disease-free interval below 12 months, more than one CRLM, largest tumor above 5 cm, and serum carcinoembryonic antigen (CEA) level above 200 μg/L.[15] In the recurrence patterns analysis, the total sum of recurrences was evaluated. The sum of rate of initial intrahepatic and initial extrahepatic recurrence exceeds the total recurrence rate since patients could have an initial intra- or extrahepatic recurrence in more than one organ.

Follow-up

During follow-up at MSKCC, serum CEA measurements and radiological imaging (abdominal and thoracic CT-scan) were performed every 3-6 months for the first three years, and yearly thereafter. In the Erasmus MC Cancer Institute follow-up was similar with radiological imaging every 3-6 months for the first two years, and yearly thereafter until 5 years.

Statistical analysis

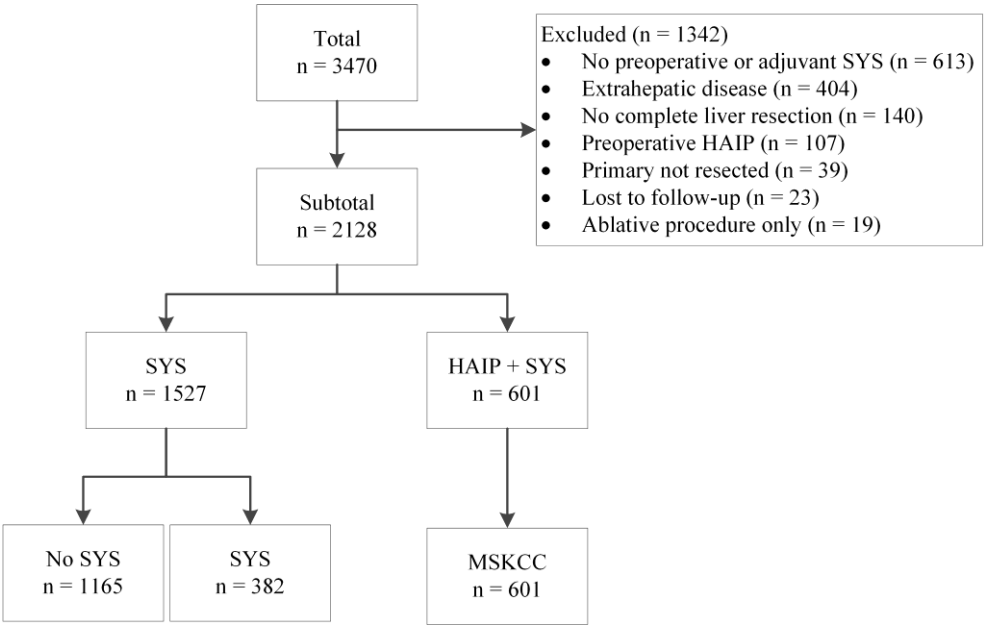
Baseline characteristic were compared using the Chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables. Median follow-up time was calculated using the reversed Kaplan-Meier method. Disease-free survival (DFS) was defined from the date of resection of CRLM until the date of recurrence, or death or last follow-up in case of no recurrence. OS was defined from the date of resection of CRLM until the date of death or last follow-up. The Kaplan-Meier method was used to calculate DFS, OS, and corresponding confidence intervals. Groups were compared using the log-rank test. Uni- and multivariable Cox regression analyses for DFS and OS were performed, and results were presented as hazard ratios (HR) with corresponding 95% confidence intervals (CIs). Cumulative incidence functions (CIF) for patients treated with HAIP and with systemic chemotherapy only were estimated using competing risk methods and compared over the entire follow-up time using Gray's test. The CIF estimates the probability of an event up to a follow-up time point *t.* The cumulative incidence was adjusted by the occurrence of the competing events. Patients developing a competing event (i.e., initial recurrence at a specific location other than the location of interest or death before developing a recurrence) were no longer at risk for the event of interest. A p-value smaller than 0.05 was considered statistically significant. Analyses were performed using SPSS (IBM Corp, version 24, Armonk, NY) and RStudio (RStudio, version 1.0.153, Boston, MA).

Results

Patients

A total of 3470 patients were evaluated for inclusion. For various reasons, 38.7% (n = 1342) of the patients were excluded (Figure 1). The two main reasons for exclusion were patients not treated with preoperative or adjuvant systemic chemotherapy (45.7%, n = 613), and the presence of EHD (30.1%, n = 404). Finally, 2128 patients were included for analysis, of which 601 patients (28.2%) received adjuvant HAIP in addition to systemic chemotherapy (HAIP + SYS). In patients treated with systemic chemotherapy only (SYS), the timing of chemotherapeutic treatment was preoperatively in 615 patients (28.9%), postoperatively in 591 patients (27.8%), and both in 922 patients (43.3%). Baseline characteristics are shown in Table 1. Patients treated with adjuvant HAIP + SYS were younger (57.2 vs. 63.0 years, $p < 0.001$), less likely to have a primary tumor of rectal origin (21.3% vs. 28.6%, $p = 0.0003$), more likely to have multiple CRLM (67.7% vs. 56.0%, $p < 0.001$), and more likely to have a high CRS (46.7% vs. 40.0%, $p = 0.005$). Also, more patients treated with HAIP + SYS received oxaliplatin- or irinotecan-based systemic chemotherapy regimens (87.4% vs. 71.0%, $p < 0.001$).

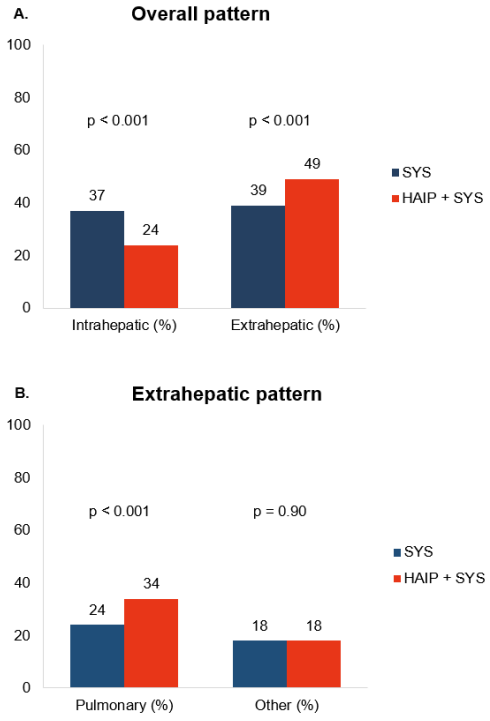
Figure 1. Study flowchart



Recurrence rates and patterns

The median follow-up for survivors was 96 months (interquartile range (IQR) 61-133 months). The median follow-up was 105 months (IQR 77-134 months) in survivors treated with HAIP + SYS and 90 months (IQR 55-131) in survivors treated with SYS only ($p < 0.001$). During follow-up 1355 patients (63.7%) developed a recurrence after resection of CRLM. In total 1204 patients (56.6%) died during follow-up. No differences were found in the overall recurrence rate in patients treated with HAIP + SYS and patients treated with SYS only (63.4% vs. 64.2%, $p = 0.74$). A lower rate of initial intrahepatic recurrences (Figure 2a) was found in patients treated with HAIP + SYS (23.6% vs. 36.8%, $p < 0.001$). In contrast, a higher rate of initial extrahepatic recurrences (Figure 2b) was found in patients treated with HAIP + SYS (49.4% vs. 39.2%, $p < 0.001$). This difference in extrahepatic recurrence was explained by a higher rate of pulmonary recurrence in the HAIP + SYS group (33.6% vs. 23.7%, $p < 0.001$). No difference was found in rates of recurrences at other extrahepatic recurrence sites (17.7% vs. 17.9%, $p = 0.90$).

Figure 2. Recurrence patterns. Overall pattern (a) Extrahepatic pattern **(b)**
Nota bene: in case of multiorgan recurrences, each organ is individually counted.



In competing risk analysis, the cumulative incidence of initial intrahepatic recurrences (Figure 3a) was significantly lower in patients treated with HAIP + SYS ($p < 0.001$). The 5-year cumulative incidence was 22.9% in the HAIP + SYS group vs. 38.4% in SYS only. The difference in cumulative incidence of intrahepatic recurrences was largely explained by a lower rate of intrahepatic recurrences in the first year after surgery (11.2% vs. 24.4%). This difference remained constant in the years thereafter.

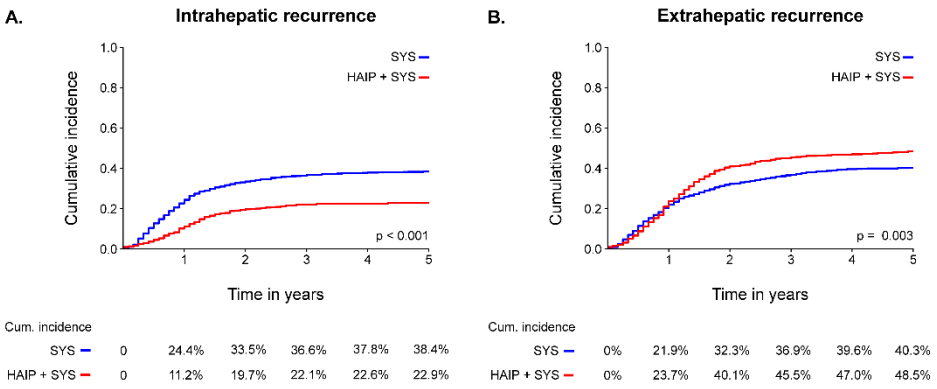
Table 1. Baseline characteristics

	All patients	**SYS**	**HAIP + SYS**	**P-value**
	n (%)	*n (%)*	*n (%)*	
Total	2128	1527	601	-
Age (median, IQR)	62 (53-69)	63.0 (54-70)	57.2 (49-66)	<0.001
Gender				0.09
Male	1275 (59.9)	932 (61.0%)	343 (57.1)	
Female	853 (40.1)	595 (39.0%)	258 (42.9)	
Primary tumor location				0.003
Right-sided	551 (26.4)	380 (25.5%)	171 (28.7)	
Left-sided	981 (47.1)	684 (45.9)	297 (49.9)	
Rectum	553 (26.5)	426 (28.6)	127 (21.3)	
Missing	43			
Nodal status primary tumor				0.57
N0	815 (38.7)	590 (39.1)	225 (37.8)	
N+	1290 (61.3)	919 (60.9)	371 (62.2)	
Missing	23			
Disease free interval				0.06
≤ 12 months	1465 (68.8)	1033 (67.6)	432 (71.9)	
> 12 months	663 (31.2)	494 (32.4)	169 (28.1)	
Number CRLM				<0.001
≤ 1	864 (40.7)	670 (44.0)	194 (32.3)	
> 1	1261 (59.3)	854 (56.0)	407 (67.7)	
Missing	3			
Size largest tumor				0.97
≤ 5cm	1612 (76.2)	1155 (76.2)	457 (76.2)	
> 5cm	503 (23.3)	360 (23.8)	143 (23.8)	
Missing	13			
CEA				0.06
≤ 200	1769 (91.2)	1233 (90.4)	536 (93.1)	
> 200	171 (8.8)	131 (9.6)	40 (6.9)	
Missing	188			
Clinical risk score				0.005
0-2	1177 (58.1%)	862 (60.0)	315 (53.3)	
3-5	850 (41.9%)	574 (40.0)	276 (46.7)	
Missing	101			

(Continued)	All patients	SYS	HAIP + SYS	P-value
Resection margin involved				0.09
No	237 (11.1)	181 (11.8)	56 (9.3)	
Yes	1881 (88.1)	1336 (87.1)	545 (90.7)	
Missing	10			
Tumor ablation at time of resection				0.97
Yes	1842 (86.6)	1322 (85.7)	520 (86.5)	
No	286 (13.4)	205 (14.3)	81 (13.5)	
SYS regimen				<0.001
Oxaliplatin or irinotecan based	443 (23.8)	370 (29.0)	73 (12.6)	
5-FU based	1415 (76.2)	907 (71.0)	508 (87.4)	
Missing	270			
Preoperative SYS				0.46
Yes	1537 (72.2)	1096 (71.8)	441 (73.4)	
No	591 (27.8)	431 (28.2)	160 (26.6)	
Center				-
MSKCC	1766 (83.0)	1165 (76.3)	601 (100)	
Erasmus MC	362 (17.0)	362 (23.7)	-	

Abbreviations: CEA: carcinoembryonic antigen; CRLM: colorectal liver metastases; CRS: clinical risk score; DFI: disease free interval; Erasmus MC: Erasmus Medical Center; HAIP: hepatic arterial infusion pump; IQR: interquartile range; MSKCC: Memorial Sloan Kettering Cancer Center; N0: lymph node negative primary tumor; N+: lymph node positive primary tumor; R1: positive resection margin; SYS: systemic chemotherapy.

Figure 3. Cumulative incidence of initial intra- and extrahepatic recurrence



The cumulative incidence of extrahepatic recurrence (Figure 3b) was comparable during the first year after surgery (23.7% vs. 21.9%). In the second year however, the cumulative incidence of initial extrahepatic recurrences was higher in patients treated with HAIP + SYS (40.1% vs. 32.3%, $p < 0.001$). At 5-years after surgery, the cumulative incidence of

extrahepatic recurrences was 48.5% in patients treated with HAIP + SYS and 40.3% in patients treated with SYS only.

Survival

Although some differences were found in baseline characteristics (Supplementary Table 1), no DFS and OS differences were found among patients from both centers treated with SYS only (Supplementary Figure 1). A superior DFS (Figure 4a) was found for patients treated with HAIP + SYS (median DFS 20 months vs. 14 months, $p < 0.001$). In multivariable Cox regressions analysis (Table 2) for DFS, HAIP + SYS remained an independent prognostic factor (adjusted HR 0.69, 95% CI 0.62-0.78, $p < 0.001$). Moreover, a superior OS was found (Figure 4b) in patients treated with HAIP + SYS (median OS 84 vs. 57 months), and HAIP + SYS was an independent prognostic factor for OS (Table 2) in multivariable analysis (adjusted HR 0.65, 95% CI 0.57-0.75, $p < 0.001$). Oxaliplatin- or irinotecan-based systemic chemotherapy was not associated with DFS (adjusted HR 1.08, 95% CI 0.94-1.25, $p = 0.29$) and OS (adjusted HR 0.92, 95% CI 0.78-1.08, $p = 0.32$) in multivariable analysis.

Figure 4. Kaplan-Meier analysis of disease-free survival (b) and overall survival (b)

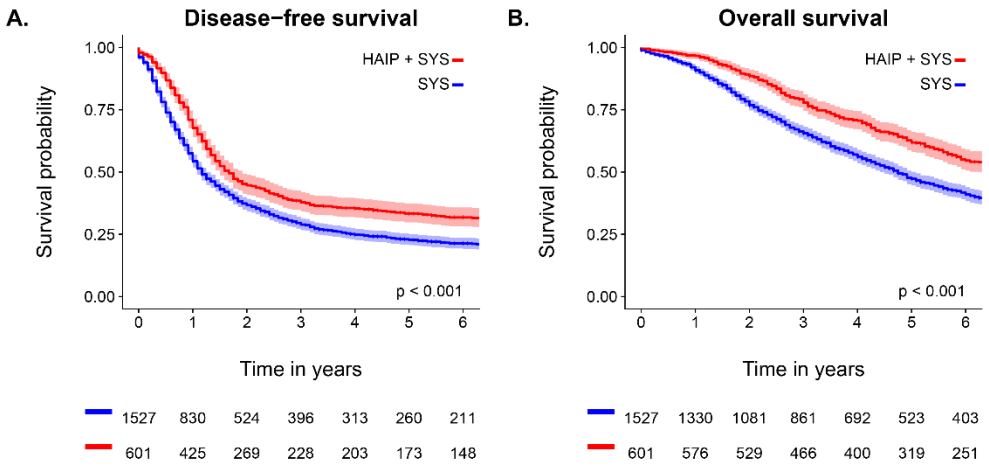


Table 2. Multivariable Cox regression analysis for disease-free survival and overall survival

Disease-free survival						
	Univariable analysis			Multivariable analysis		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
Age at resection	1.01	1.00-1.01	0.006	1.00	1.00-1.01	0.14
Year of surgery*	1.00	0.99-1.01	0.89	1.00	0.99-1.02	0.81
Right-sided tumor	1.05	0.91-1.20	0.52	1.12	0.96-1.312	0.14
Node positive primary tumor	1.42	1.28-1.58	<0.001	1.51	1.34-1.70	<0.001
Disease-free interval*	1.00	0.99-1.00	0.06	1.00	0.99-1.00	0.01
Number CRLM*	1.09	1.07-1.10	<0.001	1.11	1.09-1.13	<0.001
Diameter CRLM*	1.05	1.04-1.07	<0.001	1.06	1.04-1.08	<0.001
Preoperative CEA*	1.00	1.00-1.00	0.05	1.00	1.00-1.00	0.62
Positive resection margin	1.78	1.51-2.03	<0.001	1.60	1.35-1.90	<0.001
Center (MSKCC)	0.82	0.72-0.93	0.002	0.95	0.79-1.13	0.55
OXA- or IRINO-based SYS	0.97	0.86-1.10	0.63	1.07	0.88-1.28	0.49
HAIP + SYS	0.71	0.64-0.80	<0.001	0.69	0.60-0.79	<0.001
Overall survival						
	Univariable analysis			Multivariable analysis		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
Age at resection	1.02	1.01-1.02	<0.001	1.01	1.01-1.02	<0.001
Year of surgery*	0.97	0.96-0.98	<0.001	0.97	0.96-0.99	0.001
Right-sided tumor	1.15	0.98-1.34	0.09	1.19	1.00-1.43	0.064
Node positive primary tumor	1.48	1.32-1.67	<0.001	1.61	1.40-1.85	<0.001
Disease-free interval*	1.00	1.00-1.01	0.20	1.00	0.99-1.00	0.48
Number CRLM*	1.09	1.07-1.11	<0.001	1.11	1.08-1.13	<0.001
Diameter CRLM*	1.07	1.06-1.09	<0.001	1.07	1.05-1.09	<0.001
Preoperative CEA*	1.00	1.00-1.00	0.13	1.00	1.00-1.00	0.26
Positive resection margin	1.87	1.58-2.20	<0.001	1.74	1.43-2.11	<0.001
Center (MSKCC)	0.98	0.83-1.15	0.78	0.88	0.71-1.09	0.24
OXA- or IRINO-based SYS	0.78	0.68-0.89	<0.001	1.14	0.93-1.41	0.21
HAIP + SYS	0.65	0.57-0.74	<0.001	0.67	0.57-0.78	<0.001

Abbreviations: CEA: carcinoembryonic antigen; CRLM: colorectal liver metastases; DFI: disease free interval; HAIP: hepatic arterial infusion pump; IRINO: irinotecan, OXA: oxaliplatin, SYS: systemic chemotherapy
*Continuous

Discussion

We found that adjuvant HAIP + SYS after resection of CRLM is associated with a 1-year cumulative incidence of intrahepatic recurrence of 11.2% vs. 24.4% with SYS alone. About six patients would require treatment with adjuvant HAIP chemotherapy to avoid intrahepatic recurrence in one patient. This result is consistent with an RCT demonstrating a 2-year hepatic progression free survival of 90% in patients treated with HAIP and systemic chemotherapy (5-FU) compared to 60% in patients treated with systemic chemotherapy (5-FU) only ($p < 0.001$).[12]

Surprisingly, the substantial difference in intrahepatic recurrence rate did not translate into a difference in the percentage of patient that developed any recurrence during follow-up. After a median follow-up of 8 years, the percentage of patients who had developed any recurrence was similar (64.2% vs. 63.4%) for patients with and without adjuvant HAIP chemotherapy. However, this analysis does not consider the timing of recurrence, as well as differences in follow-up duration between treatment groups. Competing risk analysis showed that HAIP + SYS patients had a lower rate of intrahepatic recurrence within the first year and a slightly higher rate of extrahepatic recurrence after the first year. The higher rate of extrahepatic recurrence after the first year may be explained by the fact that patients who do not develop intrahepatic recurrence remain at risk for extrahepatic (in particular pulmonary) recurrence.

The percentage of patients in whom a recurrence was observed at any site was the same in the HAIP + SYS and the SYS only groups. One might than anticipate that DFS and OS are similar as well.

However, the median follow-up period in the SYS group was much shorter (90 months vs. 105 months), underestimating the true percentage of patients who had a recurrence. Moreover, the percentage of patients who develop a recurrence does not take the timing of recurrence into account. We found that the SYS patients developed a recurrence earlier during follow-up. Competing risk analysis found that SYS patients more often develop early intrahepatic recurrences, while HAIP + SYS patients more often develop late extrahepatic recurrences. These late extrahepatic recurrences are explained because HAIP + SYS patients who did not develop intrahepatic recurrence remained alive and at risk to develop extrahepatic recurrence during follow-up. The shorter follow-up period and the early onset of recurrence in the SYS group, explain the superior DFS (20 months vs. 14 months, $p < 0.001$) and OS (84 vs. 57 months, $p < 0.001$) with HAIP + SYS. These analyses demonstrate that comparison of the percentage of patients developing a recurrence during follow-up is inherently flawed: it ignores the timing of the recurrence. Consideration of time to event is essential when comparing recurrence rates and pattern of treatments.

This study has several limitations due to its retrospective design. First, systemic chemotherapy regimens varied over time and between institutions. However, modern

systemic chemotherapy has not been shown to be beneficial for OS in a large randomized controlled trial (EORTC 40983), thereby limiting potential bias by various regimes in this study.[3] Although OS was not the primary endpoint of the study, long-term follow-up demonstrated a significant difference in progression-free survival in pre-protocol analysis (20.9 months vs. 12.5 months, p = 0.035). Moreover, some studies suggest that systemic chemotherapy could be beneficial in subgroups with a high clinical risk, such as elevated CEA levels or a high CRS.[16-18]

Another study showed that survival benefit of HAIP chemotherapy was independent from modern systemic chemotherapy.[4]

Multivariable analysis of the current study did demonstrate that there was an association of the year of surgery and OS (adjusted HR 0.97, 95% CI 0.96-0.99, p = 0.001). Previous study have demonstrated that serval factors such as perioperative care and surgical techniques have improved over the years, which could possible explain our results.[19, 20] Furthermore, adjuvant HAIP chemotherapy was administered at the discretion of the medical oncologist. This could have resulted in selection of patients with favorable characteristics for adjuvant HAIP chemotherapy. However, at baseline patients that were treated with HAIP + SYS were more likely to have multiple CRLM and a high CRS compared to patients treated with SYS only. Moreover, after adjustment for known prognostic factors, administration of adjuvant HAIP chemotherapy remained strongly associated with superior DFS. Thirdly, only the initial recurrences were available for analysis. Patients who developed an initial extrahepatic recurrence may also have developed an intrahepatic recurrence several months later, and vice versa. Also, RAS status was known in only a minority of patients in this study. Therefore, we were not able to perform subgroup analyses based on KRAS mutational status. A previous study of MSKCC found the same treatment effect of HAIP in both patients with wildtype and mutated KRAS.[21] Finally, all patients treated with HAIP chemotherapy also received preoperative and/or adjuvant systemic chemotherapy. This study could not investigate the effectiveness of adjuvant HAIP chemotherapy alone, without systemic chemotherapy.
Adjuvant HAIP chemotherapy aims to avoid or delay intrahepatic recurrence after complete resection of CRLM, which should ultimately contribute to superior OS rates. About 30% of patients will never develop a recurrence after resection of CRLM; obviously, these patients do not need adjuvant HAIP chemotherapy.[2] Moreover, patients who develop early extrahepatic recurrence are also unlikely to benefit from adjuvant HAIP chemotherapy. Future studies should aim to determine which patients are most likely to benefit from adjuvant HAIP chemotherapy. Biomarkers such at circulating tumor DNA (ctDNA) and histopathological growth patterns are currently evaluated to predict the pattern of recurrence after resection of CRLM.[22, 23] A previous study found that detection of peripheral ctDNA before resection of CRLM is associated with a worse disease specific survival.[24] Peripheral ctDNA might be associated with effectiveness of perioperative treatments, this hypothesis, however, needs further research.

In conclusion, we found that patients with adjuvant HAIP chemotherapy after resection of CRLM had a lower rate of intrahepatic recurrence within the first year after surgery (11.2% vs 24.4%). Although the rate of extrahepatic recurrence after the first year was higher in patients treated with both adjuvant HAIP and systemic chemotherapy, both DFS and OS remained superior after HAIP chemotherapy which possibly could resulted from better control of liver disease.

References

1. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; 244(2):254-9.
2. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
3. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-15.
4. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017; 35(17):1938-1944.
5. Buisman FE, Homs MYV, Grunhagen DJ, et al. 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* 2019; 19(1):327.
6. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 1974; 75(4):589-96.
7. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; 30(5):969-77.
8. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983; 10(2):176-82.
9. Dizon DS, Schwartz J, Kemeny N. Regional chemotherapy: a focus on hepatic artery infusion for colorectal cancer liver metastases. *Surg Oncol Clin N Am* 2008; 17(4):759-71, viii.
10. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg* 2005; 201(1):57-65.
11. Buisman FEG, D.J.; Homs M.Y.V.; Grootscholten, C.; Filipe, W.F.; Kemeny, N.E; Cercek, AC.; D'Angelica, M.I.; Donswijk, M.L.; van Doorn, L.; Emmering, J.; Jarnagin, W.R.; Kingham, T.P.; Klompenhouwer, E.G.; Kok, N.F.M.; Kuiper, M.C.; Moelker, A.; Prevoo, W.; Versleijen, M.W.J.; Verhoef, C.; Kuhlmann, K.F.D.; Groot Koerkamp, B. Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases; results of a safety and feasibility study in The Netherlands. *Annals of Surgical Oncology (accepted for publication)* 2019.
12. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.

13. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
14. Kemeny NE, Chou JF, Boucher TM, et al. 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* 2016; 113(5):477-84.
15. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
16. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg* 2012; 255(3):534-9.
17. Ayez N, van der Stok EP, de Wilt H, et al. Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial. *BMC Cancer* 2015; 15:180.
18. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.
19. Kingham TP, Correa-Gallego C, D'Angelica MI, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. *J Am Coll Surg* 2015; 220(4):471-9.
20. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002; 236(4):397-406; discussion 406-7.
21. Gholami S, Kemeny NE, Boucher TM, et al. Adjuvant Hepatic Artery Infusion Chemotherapy is Associated With Improved Survival Regardless of KRAS Mutation Status in Patients With Resected Colorectal Liver Metastases: A Retrospective Analysis of 674 Patients. *Ann Surg* 2019.
22. van Dam PJ, van der Stok EP, Teuwen LA, et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 2017.
23. Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med* 2016; 8(346):346ra92.
24. Narayan RR, Goldman DA, Gonen M, et al. Peripheral Circulating Tumor DNA Detection Predicts Poor Outcomes After Liver Resection for Metastatic Colorectal Cancer. *Ann Surg Oncol* 2019.

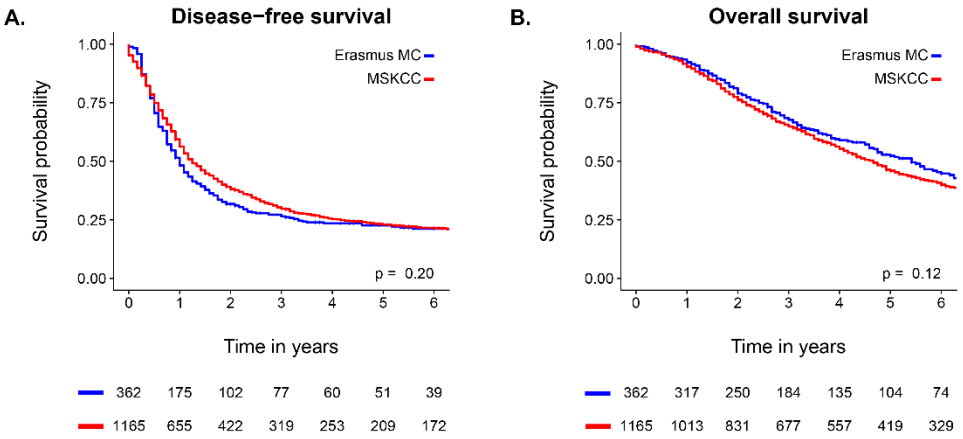
Supplementary Table 1. Baseline characteristics stratified by center

	Erasmus MC	MSKCC	P-value
	n (%)	*n (%)*	
Total	362	1766	-
Age (median, IQR)	63.0 (55.8-70.0)	61.3 (51.7-69.3)	<0.001
Gender			0.001
Male	244 (67.4)	1031 (58.4)	
Female	118 (32.6)	735 (41.6)	
Primary tumor location			<0.001
Right-sided	68 (19.2)	483 (27.9)	
Left-sided	160 (45.1)	821 (47.5)	
Rectum	127 (35.8)	426 (24.6)	
Missing	43		
Nodal status primary tumor			0.66
N0	133 (37.7)	682 (38.9)	
N+	220 (62.3)	1070 (61.1)	
Missing	23		
Disease free interval			<0.001
≤ 12 months	319 (88.1)	1146 (64.9)	
> 12 months	43 (11.9)	620(35.1)	
Number CRLM			<0.001
≤ 1	108 (30.1)	756 (42.6)	
> 1	251 (69.9)	1010 (57.2)	
Missing	3		
Size largest tumor			<0.001
≤ 5cm	312 (88.9)	1300 (73.7)	
> 5cm	39 (11.1)	464 (26.3)	
Missing	13		
CEA			0.006
≤ 200	298 (87.4)	1471 (92.0)	
> 200	43 (12.6)	128 (8.0)	
Missing	188		
Clinical risk score			<0.001
0-2	165 (49.4)	1012 (59.8)	
3-5	169 (50.6)	681 (40.2)	
Missing	10		
Resection margin involved			<0.001
Yes	65 (18.5)	172 (9.7)	
No	287 (81.5)	1594 (90.3)	
Missing	10		
Tumor ablation at time of resection			<0.001
Yes	140 (38.7)	146 (8.3)	
No	222 (61.3)	1620 (91.7)	

(Continued)	Erasmus MC	MSKCC	P-value
SYS regimen			<0.001
Oxaliplatin or irinotecan based	330 (95.4)	1085 (71.8)	
5-FU based	16 (4.6)	427 (28.2)	
Missing	270		

Abbreviations in alphabetical order: CEA: carcinoembryonic antigen; CRLM: colorectal liver metastases; CRS: clinical risk score; DFI: disease free interval; Erasmus MC: Erasmus Medical Center; HAIP: hepatic arterial infusion pump; IQR: interquartile range; MSKCC: Memorial Sloan Kettering Cancer Center; N0: lymph node negative primary tumor; N+: lymph node positive primary tumor; R1: positive resection margin; SYS: systemic chemotherapy

Supplementary Figure 1. Kaplan-Meier analysis disease-free survival and overall survival of SYS only patients stratified by center



Chapter 6

Recurrence after liver resection of colorectal liver metastases: Repeat resection or ablation followed by hepatic arterial infusion pump chemotherapy

F.E. Buisman, W.F. Filipe, N.E. Kemeny, R.R. Narayan, R.M. Srouji, V.P. Balachandran, T. Boerner, J.A. Drebin, W.R. Jarnagin, T.P Kingham, A.C. Wei, D.J. Grünhagen, C. Verhoef, B. Groot Koerkamp, M.I. D'Angelica

Annals of Surgical Oncology 2021; 28(2):808-816

Abstract

Background

The aim of this study was to investigate the effectiveness of adjuvant hepatic arterial infusion pump (HAIP) chemotherapy after complete resection or ablation of recurrent colorectal liver metastases (CRLM).

Methods

A retrospective cohort study was conducted of patients from two centers who were treated with resection and/or ablation of recurrent CRLM between 1992 and 2018. Patients with extrahepatic disease prior to or at the time of recurrence were excluded. Overall survival (OS) and hepatic disease-free survival (hDFS) were estimated using the Kaplan-Meier method. The Cox regression method was used to calculate univariable and multivariable hazard ratio's (HRs) with corresponding 95% confidence intervals (CI).

Results

Of 374 eligible patients, 81 (22%) were treated with adjuvant HAIP chemotherapy. The median follow-up for survivors was 65 months (IQR 32-118 months). Patients receiving adjuvant HAIP were more likely to have multifocal disease and receive perioperative systemic chemotherapy at time of resection for recurrence. A median hDFS of 46 months (95% CI 29-81 months) was found in patients treated with adjuvant HAIP compared to 18 months (95% CI 15-26 months) in patients treated with resection and/or ablation alone (adjusted HR 0.51, 95% CI 0.33-0.78, p = 0.002). The median OS and 5-year OS were 89 months (95% CI 52-126 months) and 66%, respectively, in patients treated with adjuvant HAIP compared to 57 months (95% CI 47-67 months) and 47%, respectively, in patients treated with resection and/or ablation only (p = 0.002). Adjuvant HAIP was associated with superior OS in multivariable analysis (adjusted HR 0.59, 95% CI 0.38-0.92, p = 0.02).

Conclusion

Adjuvant HAIP chemotherapy after resection and/or ablation of recurrent CRLM is associated with superior hDFS and OS.

Introduction

Repeat resection of colorectal liver metastases (CRLM) is safe and feasible.[1-6] Nearly half of all patients undergo re-resection and/or ablation for intrahepatic recurrences after initial resection of CRLM.[2, 7] Previous studies have demonstrated favorable overall survival (OS) for highly selected patients after repeat hepatectomy, with a 5-year OS of almost 50%.[8] Unfortunately over 60% of patients recur again, involving the liver in 65% of all patients.[6, 9] Most of these repeat recurrences occur within two years after re-intervention.[8] Effective perioperative systemic or locoregional treatments to reduce or avoid liver recurrence are needed especially in patients who have already developed liver-only recurrence.

Adjuvant hepatic arterial infusion pump (HAIP) chemotherapy improved hepatic disease-free survival (hDFS) two years after CRLM resection in a phase III trial from 60% to 90%.[10, 11] HAIP chemotherapy involves intra-arterial chemotherapy with floxuridine using a surgically implanted subcutaneous pump. The high first-pass effect of floxuridine allows for a regionally-confined high dose of chemotherapy to the liver. The rationale of adjuvant HAIP chemotherapy is that residual micrometastases in the liver after resection can be eliminated with this regional therapy.

The aim of this study was to investigate the outcomes following adjuvant HAIP chemotherapy after resection and/or ablation of recurrent CRLM in the absence of extrahepatic disease.

Methods

Patients

Consecutive treated between January 1992 and December 2018 at Memorial Sloan Kettering Cancer Center (MSKCC) or between January 2000 and December 2016 at the Erasmus MC Cancer Institute (Erasmus MC) were identified from prospectively maintained liver resection databases. Only patients with recurrent liver-only disease after prior liver resection or ablation were considered for inclusion.

Patients with incomplete resection of the primary or liver tumors were excluded, as were patients with extrahepatic disease present prior to or at the time or hepatic recurrence. Patients treated with HAIP chemotherapy at any other stage than adjuvant for recurrent CRLM were excluded. Patients treated with Stereotactic Body Radiation Therapy were also excluded.

Patients were discussed at a multidisciplinary meeting where resection, percutaneous ablation, and open ablation were considered curative-intent treatment options. Ablation included both radiofrequency and microwave ablation.

HAIP chemotherapy with floxuridine and concurrent systemic chemotherapy was administered similar as described for the use after initial resection of CRLM.[12] A maximum of 6 cycles of adjuvant HAIP chemotherapy was administered starting 4 weeks after surgery. Perioperative systemic chemotherapy was defined as any chemotherapy received within 6 months prior to or after CRLM resection. Systemic chemotherapy was offered prior to resection in patients with borderline or upfront unresectable CRLM at both centers. At MSKCC, patients with upfront resectable CRLM also received preoperative and/or adjuvant systemic chemotherapy. At Erasmus MC, only patients with early recurrence (within 6 months of primary tumor resection) typically received neoadjuvant systemic chemotherapy. A comparative survival analysis was performed to identify any differences between patients treated with perioperative systemic chemotherapy in both centers.

Definitions

Clinicopathological data were retrieved from two prospectively-maintained databases. Primary tumors were classified as right-sided if arising proximal to the splenic flexure and left-sided tumors if arising at or distal to the splenic flexure. Primary tumors arising at the rectosigmoid junction or distally were considered rectal tumors. The total number of CRLM was determined by the total number of lesions present in the resected specimen as well the total number of lesions ablated. The size of the largest tumor was similarly derived from the pathology report. The disease-free interval was calculated from the time of primary tumor resection to detection of the index CRLM. The recurrence-free interval was defined as the time of resection of the index CRLM to time of detection of the recurrent CRLM. The clinical risk score (CRS) was calculated at initial presentation and used to stratify patients into low-risk (CRS 0-2) and high-risk (CRS 3-5) of recurrence of disease.[13] The CRS is the sum of five poor prognostic factors: node-positive primary colorectal tumor, disease-free interval below 12 months, multifocal CRLM, largest tumor greater than 5 cm, and serum CEA level above 200 μg/L.[13]

Follow-up

During follow-up at MSKCC after initial hepatectomy, serum CEA measurements and radiological imaging (abdominal and thoracic) were performed every 3-6 months for the first three years, and yearly thereafter. At Erasmus MC, follow-up was similar with radiological imaging every 3-6 months for the first two years, and yearly thereafter until 5 years.

Statistical analysis

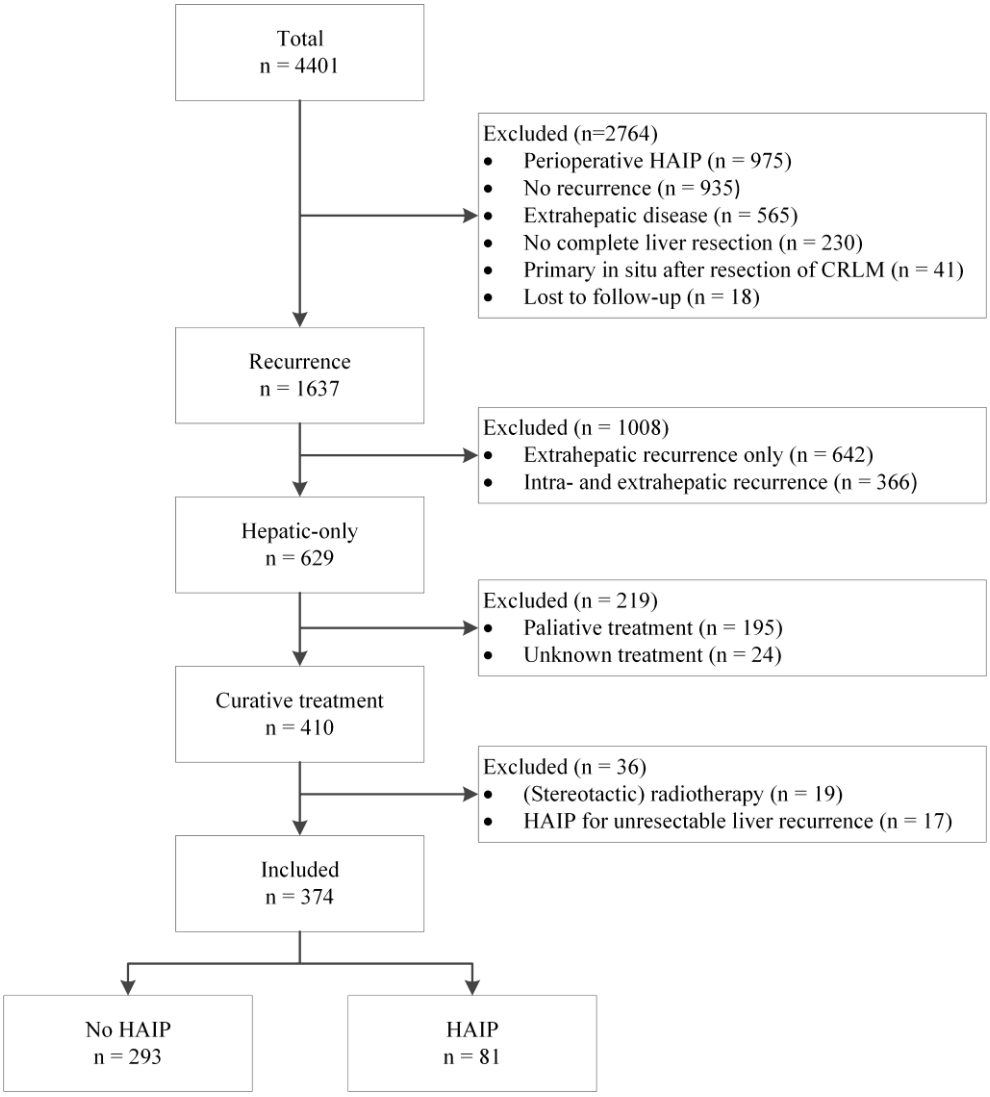
Overall survival (OS) was defined as the time from curative treatment of liver recurrence to the time of death or last follow-up, and hDFS was defined from the time of resection and/or ablation of liver recurrence to the time of subsequent liver recurrence, death, or last follow-up. Continuous variables were expressed as medians with interquartile range (IQR) and compared among groups using the Mann-Whitney U test. Categorical variables were expressed as proportions and compared among groups using the Chi-square test. Kaplan-Meier methods were used to estimate survival, and the log-rank test was used to compare survival across groups. Univariable and multivariable Cox regression analyses were performed to identify factors associated with survival. The total CRS, rather than the individual factors of the CRS, was used in the Cox regression analyses due to the limited number of events per predictor variable. Factors with a p-value of 0.20 and less were included in the multivariable model. Backward selection with stepwise elimination of factors with a p-value of more than 0.20 was performed in multivariable Cox regression analyses. A p-value less than 0.05 was considered statistically significant. Analyses were performed using SPSS (IBM Corp, version 24, Armonk, NY) and RStudio (RStudio, version 1.0.153, Boston, MA). The present study was approved by Institutional Review Boards from both centers.

Results

Patients

During the study periods, 3299 patients underwent a curative-intent treatment of CRLM at Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA) and 1102 patients at Erasmus MC Cancer Institute (Erasmus MC, Rotterdam, the Netherlands). A total of 4027 patients were excluded (Figure 1). The most common reasons for exclusion were perioperative HAIP treatment at time of index CRLM resection (n = 975, 22.2%), no recurrence noted in the study period (n = 935, 21.1%), extrahepatic recurrence only (n = 565, 12.8%), and presence of both intra- and extrahepatic recurrences (n = 366, 8.3%). The final group was comprised of 374 patients, including 81 patients (21.7%) treated with adjuvant HAIP chemotherapy. The majority of patients originated from MSKCC (n = 229, 61.2%), including all patients treated with HAIP chemotherapy.

Figure 1. Study flowchart



Patient characteristics are summarized in Table 1. HAIP patients were younger. More patients treated with HAIP chemotherapy had node positive primary tumors (n = 58, 74.4%) compared to no HAIP patients (n = 160, 55.9%; p = 0.003). The number of recurrent CRLM was higher in HAIP patients (median 2 vs. 1, p < 0.001) All patients treated with HAIP chemotherapy (n = 81, 100%) received perioperative systemic chemotherapy at time of recurrence compared to approximately one-third of patients treated with no HAIP (n = 108, 37.5%; p < 0.001).

Table 1a. Baseline characteristics

	All patients	**No HAIP**	**HAIP**	**P-value**
	n (%)	*n (%)*	*n (%)*	
Total	374	293	81	-
Patient characteristics				
Gender				0.005
Male	235	195 (66.6)	40 (49.4)	
Female	139	98 (33.4)	41 (50.6)	
Center				-
Erasmus MC	143 (38.)	143 (49.8)	-	
MSKCC	231 (61.2)	150 (51.2)	81 (100)	
Colorectal cancer				
Primary tumor location				0.24
Right-sided	78 (21.4)	56 (19.6)	22 (27.8)	
Left-sided	175 (48.1)	138 (48.4)	37 (46.8)	
Rectum	111 (30.5)	91 (31.9)	20 (25.3)	
Missing	10			
Pathologic T-stage				0.09
T1-T2	57 (16.4)	50 (18.1)	7 (9.7)	
T3-T4	291 (83.6)	226 (81.9)	65 (90.3)	
Missing	26			
Primary tumor node status				0.003
N0	146 (40.1)	126 (44.1)	20 (25.6)	
N+	218 (59.9)	160 (55.9)	58 (74.4)	
Missing	10			
Index CRLM				
Age at resection (median,	61 (53-69)	63 (56-70)	54 (46-63)	<0.001
IQR)	295 (78.9)	219 (74.7)	76 (93.8)	
<70 years	79 (21.1)	74 (25.3)	5 (6.2)	
≥70 years				
Disease-free interval				0.14
≤ 12 months	77 (20.6)	65 (22.3)	12 (14.8)	
> 12 months	296 (79.4)	227(77.7)	69 (85.2)	
	1			
Number of CRLM				0.48
1	150 (41.4)	120 (42.4)	30 (38.0)	
>1	212 (58.6)	163 (57.6)	49 (62.0)	
Missing	12			
Size of largest CRLM				0.08
≤ 5cm	296 (88.4)	230 (86.6)	66 (94.3)	
> 5cm	39 (11.6)	35 (13.4)	4 (5.7)	
Missing	39			

(Continued)	All patients	No HAIP	HAIP	P-value
Preoperative CEA				0.61
≤ 200 µg/L	281 (91.2)	228 (90.8)	53 (93.0)	
> 200 µg/L	27 (8.8)	23 (9.2)	4 (7.0)	
Missing	66			
Clinical risk score				0.09
Low-risk (0-2)	184 (56.8)	152 (59.1)	32 (47.8)	
High-risk (3-5)	140 (43.2)	105 (40.9)	35 (52.2)	
Missing	50			
Positive resection margin				0.15
Yes	46 (12.8)	38 (13.5)	7 (9.2)	
No	294 (81.9)	231 (82.2)	62 (81.6)	
RFA	19 (5.3)	12 (4.3)	7 (9.2)	
Missing	15			
Ablation at time of resection				0.46
Yes	90 (24.1)	73 (24.9)	17 (21.0)	
No	284 (75.9)	220 (75.1)	64 (79.0)	
Perioperative SYS				<0.001
Yes	277 (77.3)	203 (69.3)	74 (92.5)	
No	96 (25.7)	90 (30.7)	6 (7.5)	
Missing	1			

Abbreviations: CEA: carcinoembryonic antigen, CRLM: colorectal liver metastases, Erasmus MC: Erasmus Medical Center, MSKCC: Memorial Sloan Kettering Cancer Center, SYS: systemic chemotherapy

Table 1b. Characteristics at the time of recurrence

Recurrent CRLM	**All patients**	**No HAIP**	**HAIP**	**P-value**
	n (%)	*n (%)*	*n (%)*	
Total	374	293	81	-
Recurrence-free interval (median, IQR)	11.0 (7.0-19.3)	11.0 (7.0-20.0)	12.0 (7.0-17.0)	0.91
Number of CRLM (median, IQR)	1 (1-2)	1 (1-2)	2 (1-2)	<0.001
Missing	16			
Size of largest CRLM (median, IQR)	2.1 (1.5-3.0)	2.1 (1.5-3.1)	2.1 (1.6-2.1)	0.78
Missing	61			
CEA at recurrence (median, IQR)	6.4 (3.0-15.2)	6.9 (3.0-16.4)	6.3 (2.9-13.3)	1.00
Missing	94			
Treatment				<0.001
Resection only	252 (67.4)	175 (59.7)	77 (95.1)	
Resection with ablation	22 (5.9)	19 (6.5)	1 (1.2)	
Ablation only	100 (26.7)	99 (33.8)	3 (3.7)	
Perioperative SYS				<0.001
Yes	189 (51.2)	108 (37.5)	81 (100)	
No	180 (48.8)	180 (62.5)		
Missing	2			

Abbreviations: CEA: carcinoembryonic antigen, CRLM: colorectal liver metastases, IQR: interquartile range, SYS: systemic chemotherapy

Survival outcomes

Median follow-up for survivors was 65 months (95% CI 57-73 months), and 190 patients (50.8%) died during follow-up. Duration of follow-up was similar between HAIP patients (73 months, 95% CI 56-90) and no HAIP patients (62 months, 95% CI 52-72). No differences were found for OS (p = 0.65) in patients from both centers that were treated with perioperative systemic chemotherapy (Supplementary Figure 1). In addition, no differences were found for OS (p = 0.59) in patients that were treated with resection with/or without ablation vs. ablation only.

Hepatic disease-free survival

The median hDFS was 46 months (95% CI 29-81 months) for patients treated with HAIP chemotherapy compared to 19 months (95% CI 15-26 months) for patients treated without HAIP chemotherapy (p = 0.001, Figure 2). On univariable analysis, recurrence-free interval (HR 0.99, 95% CI 0.98-1.00, p = 0.03), preoperative CEA level at recurrence (HR 1.01, 95% CI 1.00-1.01, p = 0.01), and HAIP chemotherapy treatment (HR 0.60, 95% CI 0.43-0.82, p = 0.001) were associated with hDFS (Supplementary Table 1). On multivariable analysis, the number of CRLM at the time of recurrence (adjusted HR 1.19, 95% 1.03-1.38, p = 0.02) and

HAIP chemotherapy treatment (adjusted HR 0.51, 95% CI 0.33-0.78, p = 0.002) were the only independent prognostic factors for hDFS.

Overall survival

The median OS was 92 months (95% CI 64-120 months) for patients treated with HAIP chemotherapy compared to 57 months (95% CI 47-67 months) for patients treated without HAIP chemotherapy (p = 0.002, Figure 3). The 5-year OS was 66% in HAIP patients compared to 47% in no HAIP patients. Prognostic factors associated with OS on univariable analysis were positive resection margin at the time of index CRLM resection (HR 1.79, 95% CI 1.17-2.27, p = 0.007), elevated CEA level at recurrence (HR 1.01, 95% CI 1.00-1.01, p < 0.001), and adjuvant HAIP chemotherapy treatment (HR 0.56, 95% CI 0.38-0.82, p = 0.003, Table 2). On multivariable analysis, the CEA level at the time of recurrent CRLM detection (adjusted HR 1.01, 95% 1.00-1.01, p = 0.004) and HAIP chemotherapy treatment (adjusted HR 0.59, 95% CI 0.38-0.92, p = 0.02) remained independent prognostic factors for OS.

Figure 2. Kaplan-Meier analysis for hepatic disease-free survival

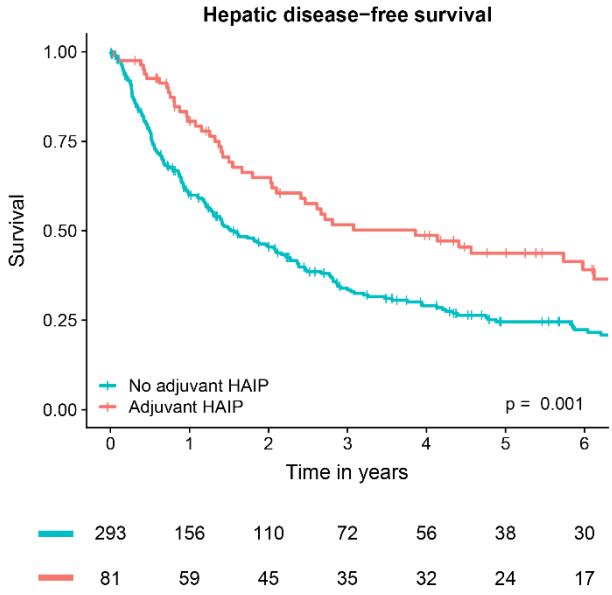


Figure 3. Kaplan-Meier analysis for overall survival

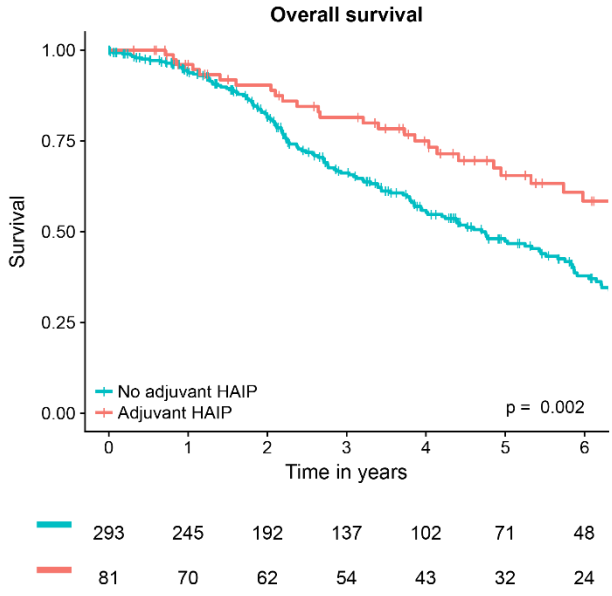


Table 2. Univariable and multivariable Cox regression analysis of factors associated with overall survival

	Univariable			Multivariable		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Index CRLM resection						
Age (>70 years)	1.27	0.89-1.81	0.19			
Right-sided tumor	0.94	0.64-1.37	0.73			
Pathologic T-stage (T3-T4)	0.97	0.64-1.47	0.89			
Clinical risk score (High)	0.97	0.71-1.34	0.87			
Resection margin (R1)	1.79	1.17-2.27	0.007	1.59	0.97-2.61	0.07
Recurrent CRLM resection						
Recurrence-free interval*	0.99	0.98-1.00	0.11			
Number of recurrent CRLM*	1.07	0.94-1.22	0.29			
Diameter of recurrent CRLM*	1.01	0.91-1.12	0.86			
CEA at recurrence*	1.01	1.00-1.01	<0.001	1.01	1.00-1.01	0.004
Perioperative SYS	1.20	0.89-1.61	0.24			
Adjuvant HAIP	0.56	0.38-0.82	0.003	0.59	0.38-0.92	0.02

Abbreviations: SYS: systemic chemotherapy, CEA: carcinoembryonic antigen, CI: confidence interval, CRLM: colorectal liver metastases, HR: hazard ratio
*Continuous

Discussion

This study found that patients receiving adjuvant HAIP chemotherapy after resection and/or ablation of recurrent CRLM had superior hDFS and OS. Patients who received adjuvant HAIP chemotherapy were younger, had more advanced disease, and were more likely to receive perioperative systemic chemotherapy. However, adjuvant HAIP chemotherapy was an independent prognostic factor in multivariable analysis for both hDFS (adjusted HR 0.51, p = 0.002) and OS (adjusted HR 0.59, p = 0.02).

In a previous study, we found that perioperative systemic chemotherapy had no impact on the intrahepatic recurrence rate after initial resection of CRLM.[14] Therefore, it seems unlikely that it would be beneficial in the setting of liver-only recurrence. Adjuvant HAIP chemotherapy has been shown to significantly decrease the hepatic recurrence rate and overall recurrence rate after initial resection of CRLM in randomized controlled trials.[10, 15] Moreover, adjuvant HAIP was associated with improved median OS from 44 months to 67 months in a retrospective study with 2368 patients.[16] Outcomes from treatment of recurrent CRLM with adjuvant HAIP chemotherapy have not been studied. The rationale for adjuvant HAIP chemotherapy after resection and/or ablation of recurrences confined to the liver is that these patients have demonstrated a propensity for liver-confined metastatic disease, which may explain the favorable results of HAIP found in our study in these patients.

The safety and effectiveness of repeat hepatectomy in selected patients have been reported in several studies.[1-6] With proper selection, repeat hepatectomy is considered safe, with similar mortality and morbidity to the initial hepatectomy. In well-selected patients, median OS after second hepatectomy has been reported to range from 32 to 43 months [2, 6, 8, 17] and 5-year OS rates ranged from 30% to 48%.[3, 6, 8] A systematic review and meta-analyses of 22-studies including 1610 patients found a median OS after hepatectomy for recurrent disease of 35 months and a 5-year OS of 42%.[6] Notably, the median OS of patients not treated with adjuvant HAIP chemotherapy in our study was 57 months, and the 5-year OS was 47%. This superior survival in our study, compared to historical cohorts, may be attributable to the strict inclusion criteria of our study, excluding patients with prior extrahepatic disease or extrahepatic recurrence at the time of intrahepatic recurrence. Patients with extrahepatic disease were excluded, because a previous study found no benefit in OS of HAIP in patients with extrahepatic disease.[16]

Previous studies identified factors associated with worse OS to include CRLM larger than 5 cm at initial hepatectomy, age below 40 years at initial hepatectomy, more than 5 liver tumors at repeat hepatectomy, and major hepatectomy at time of repeat resection.[1, 5] A concern of previous studies is their small sample size, limiting the power of their analyses. None of these previously identified prognostic factors at the time of initial hepatectomy was associated with OS in multivariable analysis in our study. In addition to the administration of HAIP chemotherapy, we also found that the margin status at the index hepatectomy and CEA level were independently associated with OS. The number of CRLM at the time of recurrence (adjusted HR 1.19, 95% 1.03-1.38, p = 0.02) and HAIP chemotherapy treatment (adjusted HR 0.51, 95% CI 0.33-0.78, p = 0.002) were the only independent prognostic factors for hDFS.

In the current study, both patients treated with resection and/or ablation were included. Two small studies compared these approaches in patients with recurrent CRLM.[4, 8] The first retrospective study evaluated 64 patients and found similar OS in patients treated with resection (n = 31, 33 months) or open/percutaneous ablation (n = 33, 33 months; p = 0.45).[4] Another retrospective study of 91 patients found similar results with a 5-year OS of 52% in patients treated with resection compared to 53% in patients treated with percutaneous ablation.[8] A limiting factor is the absence of pathological confirmation of CRLM diagnosis after ablation only procedures, which comprised one third (n = 99, 33.8%) of patients in the no HAIP group in the current study. More patients in the no HAIP group were treated with ablation only (34% vs. 4%) at time of liver recurrence. However, similar OS was found in patients treated with resection (with or without ablation) or ablation only at time of liver recurrence (p = 0.59). In addition, no difference was found in the number of ablations in the no HAIP group (n = 73, 25%) compared to the HAIP group (n = 17, 21%)(p = 0.46) at time of initial CRLM treatment.

In the present study, all patients receiving HAIP chemotherapy were concomitantly treated with systemic chemotherapy. Therefore, this study did not evaluate the effectiveness of HAIP chemotherapy alone. Moreover, different regimes were used over time due to the availability of newer chemotherapy regimens relatively recently. Limited evidence is available on the value of perioperative systemic chemotherapy in patients with repeat hepatectomy.[7] In our study, perioperative systemic chemotherapy was not associated with survival in multivariable analysis (HR 1.20, p = 0.24).

A limitation of this study was the extensive period of inclusion. During this period, the selection criteria for re-resection likely changed as well as the available perioperative systemic chemotherapy agents.[2] However, factors such as number of CRLM, size of CRLM, CEA level were included in multivariable analysis, adjusting for this time effect. Moreover, systemic chemotherapy (regardless of the regimen) was not associated with OS. Another limitation of this study was the absence of genomic data (*KRAS* and *BRAF* mutations). These genomic alterations may have influenced survival. However, previous studies have demonstrated that the effect of HAIP chemotherapy is independent of KRAS mutational studies.[18] Other studies demonstrated that RAS mutations are associated with unsalvageable recurrences after initial hepatectomy; this may also be true for subsequent recurrences after curative treatment of recurrent CRLM.[19] However, primary tumor location, which is associated with KRAS mutations and inferior survival in right-sided patients in previous studies, was included in multivariable analysis in this paper.[20] This may partly have accounted for the absence of KRAS mutational status in our study. Furthermore, it has also been shown that BRAF rarely presents with isolated and resectable disease making it unlikely that BRAF would have been a relevant factor for these patients.[21] In addition, it is unknown if treatment of subsequent recurrences differed between both centers. Since all patients treated with adjuvant HAIP chemotherapy for liver recurrence originated from MSKCC, any difference in treatment of subsequent recurrences could have introduced bias.

This is the first study reporting on the effectiveness of adjuvant HAIP chemotherapy in patients after resection and/or ablation of recurrent CRLM. Out findings suggest that a randomized controlled trial is indicated to investigate the favorable hDFS and OS of adjuvant HAIP after resection and/or ablation of recurrent CRLM.

In conclusion, this retrospective study found that HAIP is independently associated with superior hDFS and OS after resection or ablation for isolated recurrent CRLM.

References

1. Takamoto T, Hashimoto T, Miyata A, et al. Repeat Hepatectomy After Major Hepatectomy for Colorectal Liver Metastases. *J Gastrointest Surg* 2019.
2. Matsuoka H, Morise Z, Tanaka C, et al. Repeat hepatectomy with systemic chemotherapy might improve survival of recurrent liver metastasis from colorectal cancer-a retrospective observational study. *World J Surg Oncol* 2019; 17(1):33.
3. Valdimarsson VT, Hellberg K, Brismar TB, et al. Repeat procedures for recurrent colorectal liver metastases: analysis of long-term liver regeneration and outcome. *Cancer Manag Res* 2019; 11:2617-2622.
4. Dupre A, Jones RP, Diaz-Nieto R, et al. Curative-intent treatment of recurrent colorectal liver metastases: A comparison between ablation and resection. *Eur J Surg Oncol* 2017; 43(10):1901-1907.
5. Kulik U, Bektas H, Klempnauer J, et al. Repeat liver resection for colorectal metastases. *Br J Surg* 2013; 100(7):926-32.
6. Lam VW, Pang T, Laurence JM, et al. A systematic review of repeat hepatectomy for recurrent colorectal liver metastases. *J Gastrointest Surg* 2013; 17(7):1312-21.
7. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-1215.
8. Hof J, Wertenbroek MW, Peeters PM, et al. Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. *Br J Surg* 2016; 103(8):1055-62.
9. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg* 2009; 250(3):440-8.
10. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.
11. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
12. Kemeny NE, Chou JF, Boucher TM, et al. 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* 2016.
13. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
14. Buisman FE, Galjart B, van der Stok EP, et al. Recurrence Patterns After Resection of Colorectal Liver Metastasis are Modified by Perioperative Systemic Chemotherapy. *World J Surg* 2019.

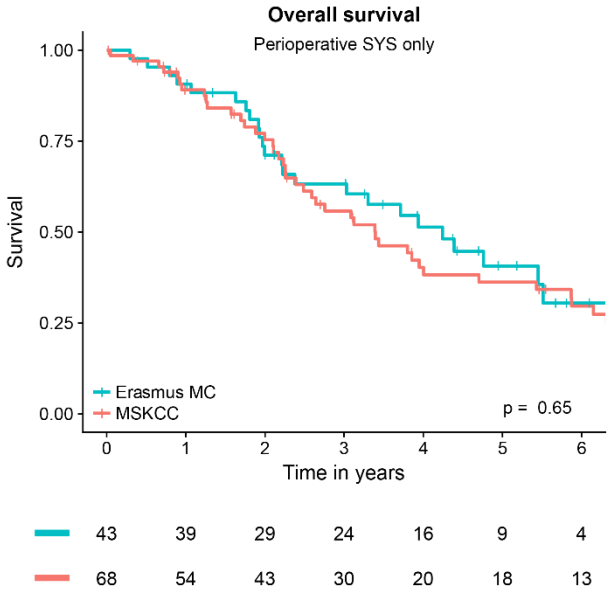
15. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy--an intergroup study. *J Clin Oncol* 2002; 20(6):1499-505.
16. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017:JCO2016718346.
17. Dupre A, Rehman A, Jones RP, et al. Validation of clinical prognostic scores for patients treated with curative-intent for recurrent colorectal liver metastases. *J Surg Oncol* 2018; 117(6):1330-1336.
18. Gholami S, Kemeny NE, Boucher TM, et al. Adjuvant Hepatic Artery Infusion Chemotherapy is Associated With Improved Survival Regardless of KRAS Mutation Status in Patients With Resected Colorectal Liver Metastases: A Retrospective Analysis of 674 Patients. *Ann Surg* 2019.
19. Okuno M, Goumard C, Kopetz S, et al. RAS Mutation is Associated with Unsalvageable Recurrence Following Hepatectomy for Colorectal Cancer Liver Metastases. *Ann Surg Oncol* 2018; 25(8):2457-2466.
20. Margonis GA, Amini N, Buettner S, et al. The Prognostic Impact of Primary Tumor Site Differs According to the KRAS Mutational Status: A Study By the International Genetic Consortium for Colorectal Liver Metastasis. *Ann Surg* 2019.
21. Gagniere J, Dupre A, Gholami SS, et al. Is Hepatectomy Justified for BRAF Mutant Colorectal Liver Metastases?: A Multi-institutional Analysis of 1497 Patients. *Ann Surg* 2018.

Supplementary Table 1. Univariable and multivariable Cox regression analysis of factors associated with hepatic disease-free survival

	Univariable			Multivariable		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Index CRLM resection						
Age (>70 years)	1.24	0.93-1.66	0.15			
Right-sided tumor	1.14	0.82-1.59	0.44			
Pathologic T-stage (T3-T4)	0.99	0.70-1.41	0.97			
Clinical risk score (High)	1.28	0.98-1.67	0.08	1.34	0.97-1.38	0.08
Resection margin (R1)	1.38	0.96-1.99	0.09			
Recurrent CRLM resection						
Recurrence-free interval*	0.99	0.98-1.00	0.03			
Number of recurrent CRLM*	1.10	0.98-1.22	0.12	1.19	1.03-1.38	0.02
Diameter of recurrent CRLM*	1.00	0.92-1.10	0.92			
CEA at recurrence*	1.01	1.00-1.01	0.01			
Perioperative SYS	0.96	0.75-1.23	0.75			
Adjuvant HAIP	0.60	0.43-0.82	0.001	0.51	0.33-0.78	0.002

Abbreviations: SYS: systemic chemotherapy, CEA: carcinoembryonic antigen, CI: confidence interval, CRLM: colorectal liver metastases, HR: hazard ratio
*Continuous

Supplementary Figure 1. Kaplan-Meier analysis for overall survival in patients treated with perioperative systemic chemotherapy stratified by center



Part II

Clinical trials on intra-arterial pump chemotherapy

Chapter 7

Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases; results of a safety and feasibility study in the Netherlands

F.E. Buisman, D.J. Grünhagen, M.Y.V. Homs, C. Grootscholten, W.F. Filipe, N.E. Kemeny, A. Cercek, M.I. D'Angelica, M.L. Donswijk, L. van Doorn, J. Emmering, W.R. Jarnagin, T.P. Kingham, E.G. Klompenhouwer, N.F.M. Kok, M.C. Kuiper, A. Moelker, W. Prevoo, M.W.J. Versleijen, C. Verhoef, K.F.D. Kuhlmann, B. Groot Koerkamp

Annals of Surgical Oncology 2019; 26(13):4599-4607

Abstract

Background

The 10-year overall survival with adjuvant hepatic arterial infusion pump (HAIP) chemotherapy after resection of CRLM was 61% in clinical trials from Memorial Sloan Kettering Cancer Center (MSKCC). A pilot study was performed to evaluate safety and feasibility of adjuvant HAIP chemotherapy in patients with resectable colorectal liver metastases (CRLM).

Study design

A phase II study was performed in two centers in the Netherlands. Patients with resectable CRLM without extrahepatic disease were eligible. All patients underwent complete resection and/or ablation of CRLM and pump implantation. Safety was determined by the 90-day HAIP-related postoperative complications from the day of pump placement (Clavien-Dindo classification, ≥ grade III) and feasibility by the successful administration of the first cycle of HAIP chemotherapy.

Results

A total of 20 patients were included with a median age 57 years (interquartile range (IQR) 51-64). Grade III or higher HAIP related postoperative complications were found in 2 patients (10%); both had a reoperation (without laparotomy) to replace a pump with a slow flow rate or to reposition a flipped pump. No arterial bleeding, arterial dissection, arterial thrombosis, extrahepatic perfusion, pump pocket hematoma, or pump pocket infections were found within 90 days after surgery. After a median of 43 days (IQR 29-52) following surgery all patients received the first dose of HAIP chemotherapy, which was completed uneventfully in all patients.

Conclusion

Pump implantation is safe and administration of HAIP chemotherapy is feasible in patients with resectable CRLM after training of a dedicated multidisciplinary team.

Introduction

Recurrent disease is reported in up to 70% of patients after resection of colorectal liver metastases (CRLM).[1] Reported 5- and 10-year overall survival (OS) of CRLM patients treated with resection and systemic chemotherapy are 40% and 25%.[1]

The rationale of adjuvant hepatic arterial infusion pump (HAIP) chemotherapy after resection of CRLM is that initial recurrences involve the liver in half of the patients. HAIP chemotherapy involves a subcutaneous surgically implanted pump that delivers chemotherapy through a catheter directly into the hepatic artery via the gastroduodenal artery. Arterial administration is preferred, because liver tumors mainly depend on arterial rather than portal venous blood supply.[2, 3] Floxuridine (or FUDR) is the preferred drug for HAIP chemotherapy. Due to its high hepatic extraction rate the intratumoral exposure is up to 400-times higher compared to systemic administration, with little or no systemic toxicity.[4] Two randomized controlled trials (RCTs) performed in the nineties demonstrated superior OS of HAIP chemotherapy. Moreover, 10-year OS of patients who received adjuvant HAIP chemotherapy in several phase II trials after 2003 was 61%.[5, 6]

Regardless of these impressive results, HAIP chemotherapy is not commonly used outside of MSKCC. One of the barriers is that floxuridine is not registered in the European Union (EU). Moreover, HAIP chemotherapy requires comprehensive training and commitment of a multidisciplinary team.

Previous studies demonstrated both safety and feasibility concerns due to its complexity requiring both technical knowledge and practical skills.[7-9] However, a previous study of 544 patients demonstrated that an experienced team was associated with less pump related complications. The pump failure rate was only 5% in the first six months after implantation.[2] HAIP-related postoperative complications include pump flow-rate abnormalities, pump dislocation, arterial bleeding, arterial dissection, arterial thrombosis, extrahepatic perfusion, pump pocket hematoma, and pump pocket infections.[8]

The aim of this study was to determine the safety and feasibility of adjuvant HAIP chemotherapy after resection of CRLM in two centers in the Netherlands.

Methods

Study design

A phase II multicenter single arm safety and feasibility study was conducted from February 2018 to February 2019 at the Erasmus MC Cancer Institute (Rotterdam) and the Netherlands Cancer Institute (Amsterdam) in the Netherlands. The Institutional Review Board approved the study protocol (MEC-2017-282). The study was registered in the Netherlands Trial Register, number: 6917.

Patients

All patients with histologically confirmed colorectal cancer and resectable CRLM without extrahepatic disease (EHD) were evaluated for inclusion. EHD was defined as any disease outside the liver prior to or at time of diagnosis of CRLM. Patients with EHD found at surgery were excluded. Patients were also excluded if positioning of a catheter for HAIP chemotherapy was not feasible based on a preoperative arterial CT-scan, prior hepatic radiation or resection, CRLM requiring two-staged resection, liver-first approach, and diagnosis of another malignancy. Positioning of a catheter was not considered feasible if the gastroduodenal artery (GDA) had no connecting branch to the left or right liver (e.g., in a patient with a completely replaced right and left hepatic artery).

Training

The initial eight implantations (4 in each center) were performed under supervision of surgeons from MSKCC (MD and TK) who both have over 10-year experience in pump implantations (i.e., a total of more than 200 implantations each). The multidisciplinary teams of both participating centers visited MSKCC for a two-day workshop. Additional training involved detailed protocols and video material of the surgical pump implantation. A PhD student attended all implantations, supervised pump refills and provided hands-on workshops for nurses and staff members.

Surgical procedure

A dedicated team of two surgeons in each center performed all implantations. Surgical resection of CRLM by laparotomy, with or without resection of the primary tumor, was combined with implantation of the HAI pump with a constant non-programmable flow rate (Tricumed IP2000V). This pump has similar specifications as the pump used in MSKCC (Codman 3000). The main difference is that the reservoir of the Tricumed pump is pressurized by butane rather than Freon, which is not allowed in the EU due to environmental laws. Treatment of the CRLM involved complete resection and/or open ablation. In case of a simultaneous resection of the primary tumor, liver resection with pump implantation was performed first, followed by resection of the primary tumor to prevent contamination of the pump. Prior to pump implantation a function test was performed to check adequate operation of the pump. A cholecystectomy was performed to avoid cholecystitis as a result of intra-arterial chemotherapy through the cystic artery.[10] The pump pocket was created at the left-

lower quadrant of the abdominal wall, or in the right-lower quadrant in patients with a colostomy. The pocket cavity was created three-quarters caudal to the incision to ensure easy access of the pump septum for percutaneous refills.

The entire GDA, and the proximal proper hepatic artery were mobilized and dissected circumferentially from their attachments to facilitate insertion of the catheter and to avoid inadvertent perfusion of the pancreas, stomach, or duodenum. The distal GDA was ligated with a nonabsorbable tie and a transversal arteriotomy was performed followed by insertion of the catheter. The catheter was positioned just at the origin of the GDA. Positioning on the catheter with the tip in the hepatic artery may cause turbulence and the risk of thrombosis, while positioning of the catheter too far from the hepatic artery may cause pooling of floxuridine in the GDA with risk of erosion, a pseudoaneurysm and hemorrhage. A metal connector was used to connect a commercially available (B. Braun Celsite®) intra-arterial catheter (distal catheter) with the Tricumed catheter that comes with the pump (Tricumed Catheter 1000®). This connection was secured with two non-absorbable ties. The distal catheter has several beads (i.e., local thickening of the catheter wall), which were used to secure the catheter with non-absorbable ties in the GDA. Perfusion of both lobes of the liver and lack of extrahepatic perfusion was confirmed by an intraoperative bolus injection of methylene blue. After the perfusion test, the catheter was flushed with heparinized saline, and the wounds were closed. Any replaced and accessory hepatic arteries were ligated, provided that a patent GDA connected with at least one hepatic artery was present. Intrahepatic shunts will typically reassure that the catheter perfuses all liver segments, which was confirmed intraoperatively, and during follow-up with postoperative scintigraphy.

Postoperative procedures

Prior to the start of HAIP chemotherapy a postoperative technetium-99-labeled macroaggregated albumin (Tc-99m MAA) scintigraphy was performed to confirm again the absence of extrahepatic perfusion. In case of extrahepatic perfusion, patients were evaluated angiographically and branches were embolized with re-testing prior to start of treatment.

Chemotherapeutical regime

HAIP chemotherapy was initiated 4-12 weeks after surgery depending on patients' condition and liver function. 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 chemotherapy to prevent thrombosis of the catheter. All patients were scheduled for 6 cycles of 4 weeks of HAIP chemotherapy with floxuridine. Each cycle comprised of 2 weeks of HAIP chemotherapy followed by a two weeks rest period during which the pump was filled with the heparinized saline solution. Floxuridine was dosed based upon the MSKCC regime (0.12 mg/kg per day).[11, 12] If the actual weight was more than 25% above the ideal weight, the dose of floxuridine was calculated using the average of the actual and ideal weight. Floxuridine was administered in a solution of 35.000 IE heparin and 25 mg dexamethasone in NaCl 0.9% with a total volume of 35 mL. A prophylactic dose of 20 mg proton pump inhibiters was administered daily during HAIP

chemotherapy. No adjuvant systemic chemotherapy was administered, since this is not the standard of care in the Netherlands.

Outcomes

Safety was determined by the percentage of postoperative complications (Clavien-Dindo classification, grade III or higher) within 90 days after surgery related to HAI pump placement. The feasibility was defined as the percentage of patients receiving at least one cycle of adjuvant HAIP chemotherapy after resection of CRLM.

Definitions and statistical analysis

Demographic and clinicopathological characteristics were presented as medians with interquartile range (IQR) and as means with ranges for continuous variables and proportions for categorical variables. CRLM that were detected within three months of resection of the primary tumor were considered synchronous. Any chemotherapy administered within 3 months prior to resection was considered as preoperative chemotherapy. A positive resection margin (R1) was defined as tumor cells present at the resection margin. Major liver resection was defined as complete resection of ≥ 3 segments. All analyses were performed using SPSS (IBM Corp, version 24, Armonk, NY).

Results

A total of 22 patients were included in two centers (Erasmus MC Cancer Institute and the Netherlands Cancer Institute) from February 2018 until February 2019 in the Netherlands. Two patients were excluded during surgery; one patient had unresectable CRLM found during intra-operative ultrasonography, and one patient was excluded due to an occult peritoneal lesion that was found during surgery and confirmed by a frozen section biopsy. No patients were excluded due to unexpected abnormal hepatic artery anatomy. A total of 20 patients were eligible.

Baseline characteristics

Baseline characteristics of 20 patients that were eligible for surgical treatment and pump implantation are shown in Table 1. Median age was 57 years (IQR 51 – 64 years), and the majority of patients were male (n = 12, 60%). Most patients had left-sided colorectal cancer (n = 11, 55%), followed by rectal (n = 6, 30%), and right-sided colorectal cancer (n = 3, 15%). About half of the patients had synchronous CRLM (n = 11, 55%).

Surgical aspects

Surgical aspects are summarized in Table 2. Preoperative chemotherapy was administered in seven patients (35%). In four patients (20%) the procedure was combined with simultaneous resection of the primary tumor. In seven patients (35%) ablation was combined with

resection. In two patients (10%) only open ablation and pump implantation were performed. A major liver resection was performed in four patients (20%). The hepatic arterial anatomy was abnormal in 10 patients (50%), requiring ligation of accessory or replaced left and/or right hepatic arteries. The pump was positioned in the left lower quadrant of the abdomen in 18 patients (90%). The right-lower abdomen was the preferred site in two patients (10%) due to a prior colostomy in the left lower quadrant. The median hospital stay was 8 days (IQR 6-9 days). Postoperative Tch-99m MAA scintigraphy showed no signs of extrahepatic perfusion in all patients.

Postoperative complications

Postoperative complications are summarized in Table 3. No postoperative 90-day mortality was found. No arterial bleeding, arterial dissection, arterial thrombosis, pump pocket hematoma, or pump pocket infections were found within the first 90-days after surgery. Five patients (25%) had postoperative complications of grade III or higher. Two patients (10%) had complications related to HAI pump placement. The first patient required pump replacement due to a decreased flow rate of the pump and the second patient had a flipped pump (upside-down) requiring reoperation. In both patients, reoperation involved a local exploration of the pump pocket without a laparotomy with same day discharge. Both patients recovered uneventful and continued HAIP chemotherapy within two weeks.

Another three patients (15%) required re-interventions due to complications unrelated to HAI pump implantation. One patient required a re-laparotomy for biliary peritonitis as a result of biliary leakage at the liver resection margin, and a second re-laparotomy due to fascial dehiscence. A second patient was readmitted with an intra-abdominal fluid collection that was treated with both percutaneous drainage and intravenous antibiotics. The third patient was readmitted for percutaneous drainage of an intra-abdominal fluid collection with negative culture. All three patients recovered uneventful.

Initiation of HAIP chemotherapy

The median period to administration of the first cycle of HAIP chemotherapy was 43 days (IQR 29-52 days). Percutaneous access of the pump for the first cycle of HAIP chemotherapy was performed without adverse events in all patients. All patients uneventfully completed the first cycle of HAIP chemotherapy, which was the primary endpoint for feasibility.

Table 1. Baseline characteristics

	Age (y)	Gender	ASA Score	BMI (kg/m^2)	Location CRC	T-stage CRC	Nodal status	Synchronous / Metachronous	DFI (m)	No. CRLM	Size largest CRLM (cm)	CEA (µg/L)
Median (IQR); n (%)	57 (51-64)	Male: 12 (60%)	2 (1-2)	27 (24-27)	Right: 3 (15%)	3 (3-4)	N0: 6 (30%)	Syn: 11 (55%)	1 (0-13)	2 (1-5)	2.3 (0.8-7.1)	6 (3-26)
Case 1	58	Female	3	27	Rectum	3	0	Metachronous	6	1	6.7	23
Case 2	64	Male	2	34	Left	3	2	Metachronous	41	3	2.4	6
Case 3	52	Female	2	29	Left	3	1	Metachronous	13	1	2.8	5
Case 4	64	Male	3	24	Left	3	1	Metachronous	13	1	1.8	5
Case 5	75	Female	2	26	Left	3	0	Synchronous	0	1	2.2	8
Case 6	67	Male	1	24	Left	4	0	Synchronous	0	2	4.8	34
Case 7	50	Female	1	24	Left	3	0	Synchronous	2	2	2.0	63
Case 8	54	Male	3	24	Right	4	2	Metachronous	28	2	2.3	27
Case 9	68	Male	2	24	Right	4	2	Synchronous	0	5	1.2	40
Case 10	58	Male	2	25	Left	3	1	Synchronous	0	5	7.1	2
Case 11	57	Female	2	25	Left	4	2	Metachronous	15	2	4.8	1
Case 12	66	Male	3	23	Left	4	1	Synchronous	0	4	4.2	24
Case 13	51	Female	1	27	Rectum	3	1	Metachronous	2	5	1.3	3.
Case 14	42	Female	1	23	Left	3	0	Metachronous	4	13	1.5	3
Case 15	54	Female	1	25	Right	3	1	Synchronous	0	3	2.5	19
Case 16	61	Male	2	25	Left	3	1	Synchronous	0	2	1.6	3
Case 17	54	Male	2	28	Rectum	3	1	Synchronous	0	7	52	880
Case 18	43	Male	1	25	Rectum	2	1	Synchronous	0	12	0.8	4
Case 19	57	Male	1	24	Rectum	3	0	Metachronous	12	2	2.2	6
Case 20	46	Male	2	24	Rectum	2	1	Synchronous	0	1	1.0	3

Abbreviations: ASA: American Society of Anesthesiologist Score, BMI: body mass index, CEA: carcinoembryonic antigen, CRC: colorectal cancer, CRLM: colorectal liver metastasis, DFI: disease-free interval, IQR: interquartile range, N0: node negative, Syn: synchronous, T-stage CRC: tumor-stage colorectal cancer

Table 2. Surgical outcomes

	Procedure	Preoperative CTx	Resection/ ablation	Major resection	Hepatic arterial anatomy	Resection margin	Operative time (min.)	Blood loss (mL)	Hospital stay	Days to start HAIP
Median (IQR); n(%)	Primary first: 4 (20%)	Yes: 7 (35%)	Resection only: 11 (55%)	Yes: 4 (20%)	Abnormal: 10 (50%)	R1: 4 (20%)	226 (187-290)	610 (200-838)	8 (6-9)	43 (29-52)
Case 1	Primary first	No	R	No	Normal	R0	169	0	7	41
Case 2	Primary first	No	R	No	Abnormal	R1	204	1360	6	55
Case 3	Primary first	No	A	No	Normal	Ablation	161	0	6	54
Case 4	Primary first	Yes	R	No	Abnormal	R1	176	280	7	47
Case 5	Simultaneous*	No	R	No	Normal	R0	204	560	6	28
Case 6	Simultaneous*	Yes	R	No	Abnormal	R0	351	2850	31	56
Case 7	Primary first	No	R +A	Yes	Abnormal	R0	246	800	9	43
Case 8	Primary first	No	R	No	Normal	R0	180	710	10	43
Case 9	Primary first	Yes	R	No	Abnormal	R1	283	2000	7	41
Case 10	Primary first	Yes	R	Yes	Normal	R0	331	1700	8	57
Case 11	Primary first	Yes	R	Yes	Normal	R0	241	750	9	55
Case 12	Simultaneous*	No	R +A	No	Normal	R0	316	0	9	42
Case 13	Primary first	No	R +A	No	Normal	R0	315	620	6	26
Case 14	Primary first	Yes	R +A	Yes	Abnormal	R0	267	600	9	29
Case 15	Primary first	Yes	R	No	Normal	R1	188	650	5	29
Case 16	Primary first	No	A	No	Abnormal	Ablation	206	200	4	43
Case 17	Simultaneous†	No	R +A	No	Abnormal	R0	287	850	9	43
Case 18	Primary first	No	R +A	No	Abnormal	R0	291	150	7	29
Case 19	Primary first	No	R +A	No	Normal	R0	186	200	9	27
Case 20	Primary first	No	R	No	Normal	R0	210	200	8	27

Abbreviations: A: ablation, CTx: chemotherapy, HAIP: hepatic arterial infusion pump, IQR: interquartile range, R: resection, R1: irradical resection margin

* Sigmoid resection

† Low anterior resection

Table 3. Postoperative complications within 90-days of surgery

	≥ Grade III (Clavien-Dindo)	HAI pump related	Time to event (d)	Requiring readmission	Requiring surgery	Specified
Total (%)	5 (25%)	2 (10%)		4 (20%)	3 (15%)	
Case 1	-					
Case 2	IIIb	Yes	42	Yes	Yes	Pump replacement due to slow flow rate
Case 3	IIIb	Yes	41	Yes	Yes	Flipped pump
Case 4	-					
Case 5	-					
Case 6	IVa	No	4	No	Yes (2x)	1. Biliary peritonitis due to leakage at liver resection margin 2. Threatening abdominal fascial dehiscence
Case 7	-					
Case 8	-					
Case 9	-					
Case 10	IIIa	No	13	Yes	No	Percutaneous drainage of sterile abdominal fluid collection
Case 11	IIIa	No	9	Yes	No	Spontaneous bacterial peritonitis requiring antibiotics and percutaneous drainage
Case 12	-					
Case 13	-					
Case 14	-					
Case 15	-					
Case 16	-					
Case 17	-					
Case 18	-					
Case 19	-					
Case 20	-					

Abbreviations: HAI: hepatic arterial infusion

Discussion

This study demonstrated that HAI pump implantation and administration of adjuvant HAIP chemotherapy in patients with resectable CRLM is safe and feasible in the Netherlands. Safety was demonstrated with two patients (10%) developing HAIP-related postoperative complications that were resolved with a reoperation to replace or reposition the subcutaneous pump. Feasibility was demonstrated because all patients started HAIP chemotherapy within six weeks after surgery.

As a result of the pump with a decreased flow-rate, the preimplantation pump performance test procedure was adapted. The pump flow-rate is temperature dependent, reaching optimal flow-rates at body temperature. The new pump performance test included continuous heating of the pump to 37 degrees Celsius within an ex-vivo heater allowing precise observation of pump flow-rate mimicking in-vivo conditions. In order to minimize the risk of pump dislocation (flipping within the pump pocket), all pockets were created with minimal residual space in order to achieve a tight fit with minimal risk of dislocation of the infusion pump in the pocket. In obese patients (i.e., BMI >30) we prefer to position the pump on the chest wall. The observed complication rate seems acceptable compared to a large retrospective study, in which 544 patients that underwent pump implantation for CRLM were evaluated.[8] Pump related complications were reported in 120 patients (22%) and were classified as related to the hepatic arterial system (n = 62, 51%), the catheter (n = 33, 26%), the pump-pocket (n = 19, 16%), or the pump (n = 6, 5%). Technical complications could be salvaged in 54 patients (45%). A higher rate of complications was found with surgeons that performed less than 25 implantations (31% vs. 19%, $p < 0.001$). Other perioperative factors were comparable with our study: mean operative time (260 minutes vs. 241 minutes in our study), mean blood loss (490 mL and 724 mL in our study), and length of hospital stay (8 days vs. 9 days in our study). However, long-term follow-up is needed for complete comparison of our results with this study.

Our multidisciplinary approach with extensive training and proctoring by MSKCC was essential for the safety and feasibility of setting up a HAIP chemotherapy program. In a previous RCT on hepatic arterial infusion chemotherapy, lack of training and experience appeared to be the major factor for failure of safety and feasibility.[7] Lorenz et al. compared resection of CRLM combined with adjuvant hepatic arterial infusion (HAI) of 5-FU with resection of CRLM alone. The trial was prematurely terminated after interim analysis for futility. At the time of interim analysis, a total of 113 were randomized into each group. Eight patients (7%) within the HAI group died within 30-days after surgery; four deaths were related to HAI chemotherapy toxicity, three to catheter related bleeding, and one to angiography induced shock. In the control group three patients (3%) died within 30-days. High rates of drop-outs, i.e. patients that did not receive the assigned treatment, were reported in both groups with various reasons: 24 patients (21%) assigned to HAI + resection (no catheter implanted (n = 7), CRLM not resected (n = 6), malperfusion (n = 5), refusal of patient

(n = 2), port complications (n = 2), port complications ($n = 2$), liver cirrhosis (n = 1), postoperative ileus (n = 1)), and 13 patients (12%) assigned to resection alone (CRLM not resected (n = 10), and residual disease after resection (n = 3)). Explanations that could have accounted for the failure of this trial were: participation of 26 centers with each center performing only about 1 intra-arterial catheter placement per year, the use of a port with a catheter in the flow of the hepatic artery resulting in a high rate of technical failures (e.g., hepatic arterial thrombosis), and the use of intra-arterial 5-FU, which is not only less effective (lower dose due to smaller first-pass effect), but also has a much higher systemic exposure compared to floxuridine.[4]

Several studies, including an RCT, demonstrated superior survival of HAIP chemotherapy compared to systemic chemotherapy alone in patients with resectable CRLM.[5, 6, 13, 14] A phase III RCT for adjuvant HAIP chemotherapy found an improvement in 2-year survival (86% vs. 72%, p = 0.03).[13] Long-term follow-up of 287 patients receiving adjuvant HAIP chemotherapy in four prospective trials at MSKCC demonstrated a 10-year OS of 61%.[5] A recent propensity scored analysis demonstrated an OS benefit of 23 months of adjuvant HAIP chemotherapy compared to systemic chemotherapy alone (67 month vs. 44 months, p < 0.001).[14] The OS without HAIP was similar with other large cohorts outside MSKCC.[15] The difference remained at propensity score analysis with an adjusted hazard ratio of 0.67 (95% CI, 0.59-0.76, p < 0.001).

Implementation of HAIP chemotherapy beyond MSKCC is currently limited to a few centers in the world (e.g., University Hospital Zurich (Zurich, Switzerland), University of *Pittsburgh* Medical Center (Pittsburgh, USA), and Washington University School of Medicine (*St. Louis, USA)).* Several explanations have been suggested that could account for this. The historical perspective may be partly responsible. The first trials on HAIP chemotherapy date from the nineties, a decade in which new promising agents for systemic chemotherapy such as irinotecan and oxaliplatin were introduced. Administration of intravenous drugs was simple compared to implementation of HAIP chemotherapy that required new skills and close collaboration within multidisciplinary teams. Modern systemic chemotherapy results in superior survival in selected patients with stage IV CRC.[16, 17] In the subgroup of patients with resectable CRLM, no OS benefit was found (p = 0.30) in a phase III RCT, although progression-free survival was superior in the per protocol analysis (p = 0.035).[18] Despite these results the recurrence rate was still about 70%. This disappointing high percentage of recurrent disease after curative resection of CRLM and perioperative systemic chemotherapy has renewed interest in adjuvant HAIP chemotherapy.

Secondly, regulatory factors have also opposed implementation of HAIP chemotherapy outside the US. Floxuridine was first registered by the FDA in 1971, in the EU however, floxuridine can't be used outside clinical trials since it is not registered. Others have resorted to 5-FU or oxaliplatin instead of floxuridine. A previous trial on intermittent infusion of 5-FU through a mediport in the hepatic artery was terminated prematurely, mainly due to a high

rate of 5-FU related complications.[7] The hallmark of HAIP chemotherapy, however, is the 95% first-pass effect of floxuridine in the liver that allows for a very high dosage with continuous infusion without systemic toxicity.

No infusion pump with the intended use of intra-arterial chemotherapy is currently registered in the EU. The Tricumed IP2000V infusion pump is CE marked and has been used for many years in patients with spasticity and chronic pain. Both registration of floxuridine and an infusion pump for HAIP chemotherapy are essential steps for implementation of this treatment in the EU. The subcutaneous pump is a key component of the intra-arterial chemotherapy, because floxuridine has a half-life of only 10 minutes.[4] A percutaneous approach for delivery of intra-arterial chemotherapy is investigated by the Gustave Roussy hospital in Paris (France).[19] Goeré et al administered intra-arterial oxaliplatin using a percutaneous catheter in the hepatic artery. With the percutaneous approach, a catheter remains positioned in the flow of the hepatic artery with a higher risk of hepatic artery thrombosis. Therefore, the percutaneous approach is not suitable for prolonged administration. The pump has an intra-arterial catheter in the gastroduodenal artery, outside the hepatic arterial flow and therefore less likely to cause thrombosis. The pump can stay in for many years for treatment of disease recurrence in the liver. Furthermore, the surgical approach allows complete circumferential dissection of the artery, which is important to avoid complications of extrahepatic perfusion of floxuridine. The potential effects of extrahepatic perfusion of floxuridine are more severe than the effects of extrahepatic perfusion of oxaliplatin due to the high dose of floxuridine administered compared to oxaliplatin provided by its high first-pass effect.

Conclusions

This is the first study prospectively reporting early safety and feasibility results on adjuvant HAIP chemotherapy in patients with resectable CRLM. Some fundamental elements have been considered in the design of our program including, thorough training on all safety and technical aspects, selection of appropriate materials, and careful selection of patients and participating centers. The number of participating centers for the safety and feasibility study was only two to guarantee adequate training and experience. All future implantations will be performed by a team of two experienced surgeons, and new surgeons will only be allowed to perform implantations after thorough training to sustain knowledge and skills.

After confirming safety and feasibility, we have proceeded with a multicenter phase III RCT (The PUMP trial) to study the effectiveness of adjuvant HAIP chemotherapy in patients with resectable CRLM (www.trialregister.nl, NTR7493).[20]

In conclusion, this study showed that starting a HAIP chemotherapy program can be safe and feasible after adequate training and proctoring of a multidisciplinary team.

References

1. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4:283-301.
2. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 1974; 75(4):589-96.
3. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; 30(5):969-77.
4. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983; 10(2):176-82.
5. Kemeny NE, Chou JF, Boucher TM, et al. 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* 2016; 113(5):477-84.
6. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
7. Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg* 1998; 228(6):756-62.
8. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg* 2005; 201(1):57-65.
9. Chakedis J, Beal EW, Sun S, et al. Implementation and early outcomes for a surgeon-directed hepatic arterial infusion pump program for colorectal liver metastases. *J Surg Oncol* 2018; 118(7):1065-1073.
10. Kemeny MM, Goldberg D, Beatty JD, et al. Results of a prospective randomized trial of continuous regional chemotherapy and hepatic resection as treatment of hepatic metastases from colorectal primaries. *Cancer* 1986; 57(3):492-8.
11. Ammori JB, Kemeny NE. Regional hepatic chemotherapies in treatment of colorectal cancer metastases to the liver. *Semin Oncol* 2010; 37(2):139-48.
12. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. *Mol Cancer Ther* 2009; 8(5):1015-1025.
13. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.
14. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017:JCO2016718346.

15. Hamady ZZ, Lodge JP, Welsh FK, et al. One-millimeter cancer-free margin is curative for colorectal liver metastases: a propensity score case-match approach. *Ann Surg* 2014; 259(3):543-8.
16. Masi G, Loupakis F, Pollina L, et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. *Ann Surg* 2009; 249(3):420-5.
17. Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; 370(9582):143-152.
18. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-15.
19. Goere D, Pignon JP, Gelli M, et al. 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* 2018; 18(1):787.
20. Buisman FE, Homs MYV, Grunhagen DJ, et al. 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* 2019; 19(1):327.

Chapter 8

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

F.E. Buisman, M.Y.V. Homs, D.J. Grünhagen, W.F. Filipe, R.J. Bennink, M.G.H. Besselink, I.H.M. Borel Rinkes, R.C.G. Bruijnen, A. Cercek, M.I. D'Angelica, O.M. van Delden, M.L. Donswijk, L. van Doorn, P.G. Doornebosch, J. Emmering, J.I. Erdmann, N.S. IJzerman, C. Grootscholten, J. Hagendoorn, N.E. Kemeny, T.P. Kingham, E.G. Klompenhouwer, N.F.M. Kok, S. Koolen, K.F.D. Kuhlmann, M.C. Kuiper, M.G.E. Lam, R.H.J. Mathijssen, A. Moelker, E. Oomen-de Hoop, C.J.A. Punt, W.W. te Riele, J.M.L. Roodhart, R.J. Swijnenburg, W. Prevoo, P.J. Tanis, M. Vermaas, M.W.J. Versleijen, F.P. Veuger, M.J. Weterman, C. Verhoef, B. Groot Koerkamp

BMC Cancer 2019;19(10):327

Abstract

Background

Recurrences are reported in 70% of all patients after resection of colorectal liver metastases (CRLM), in which half are confined to the liver. Adjuvant hepatic arterial infusion pump (HAIP) chemotherapy aims to reduce the risk of intrahepatic recurrence. A large retrospective propensity score analysis demonstrated that HAIP chemotherapy is particularly effective in patients with low-risk oncological features. The aim of this randomized controlled trial (RCT) - the PUMP trial - is to investigate the efficacy of adjuvant HAIP chemotherapy in low-risk patients with resectable CRLM.

Methods

This is an open label multicenter RCT. A total of 230 patients with resectable CRLM without extrahepatic disease will be included. Only patients with a clinical risk score (CRS) of 0 to 2 are eligible, meaning: patients are allowed to have no more than two out of five poor prognostic factors (disease-free interval less than 12 months, node-positive colorectal cancer, more than 1 CRLM, largest CRLM more than 5 cm in diameter, serum carcinoembryonic antigen above 200 μg/L). Patients randomized to arm A undergo complete resection of CRLM without any adjuvant treatment, which is the standard of care in the Netherlands. Patients in arm B receive an implantable pump at the time of CRLM resection and start adjuvant HAIP chemotherapy 4-12 weeks after surgery, with 6 cycles of floxuridine scheduled. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival, hepatic PFS, safety, quality of life, and cost-effectiveness. Pharmacokinetics of intra-arterial administration of floxuridine will be investigated as well as predictive biomarkers for the efficacy of HAIP chemotherapy. In a side study, the accuracy of CT angiography will be compared to radionuclide scintigraphy to detect extrahepatic perfusion. We hypothesize that adjuvant HAIP chemotherapy leads to improved survival, improved quality of life, and a reduction of costs, compared to resection alone.

Discussion

If this PUMP trial demonstrates that adjuvant HAIP chemotherapy improves survival in low-risk patients, this treatment approach may be implemented in the standard of care of patients with resected CRLM since adjuvant systemic chemotherapy alone has not improved survival.

Trial registration

The PUMP trial is registered in the Netherlands Trial Register (NTR), number: 7493. Date of registration September 23 2018.

Background

Colorectal cancer (CRC) is the third most common cancer in the Netherlands. More than half of patients with CRC will eventually develop colorectal liver metastases (CRLM), of whom 25% have resectable disease at first presentation.[1] Most patients develop recurrent disease after curative intent resection of CRLM, which in about 50% of patients is confined to the liver.[2] A large phase III trial investigating perioperative systemic chemotherapy for patients with resectable CRLM found overlapping survival curves: 5-year overall survival (OS) was 51% with perioperative chemotherapy versus 48% with surgery alone ($p = 0.34$).[3, 4] Therefore, resection without additional chemotherapy is currently the standard of care in the Netherlands and better adjuvant treatment is needed.

The risk of recurrence can be predicted with the clinical risk score (CRS).[5] The CRS is the sum of five poor prognostic factors: disease-free interval less than 12 months, node-positive, more than one CRLM, largest CRLM over 5 cm in diameter, and serum carcinoembryonic antigen (CEA) level above 200 µg/L. After assigning one point to each of the five risk factors, patients can be stratified into low-risk (0-2 points) and high-risk (3-5 points) of recurrence.

Hepatic arterial infusion pump chemotherapy

Hepatic arterial infusion pump (HAIP) chemotherapy using floxuridine 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 (EU), because floxuridine is not registered in the EU. The biological rationale for intra-arterial treatment is that the hepatic artery rather than the portal vein is responsible for most of the blood supply to liver tumors.[6, 7] Intra-arterial floxuridine (FUDR) is delivered in the hepatic artery via a surgically implantable pump with a catheter in the gastroduodenal artery. Up to 95% of floxuridine is extracted by the liver during the first-pass, allowing an up to 400-fold increase in hepatic exposure with minimal systemic exposure.[8, 9] The pump is filled percutaneously and the liver is continuously perfused with chemotherapy.

Promising results of HAIP chemotherapy have been reported. A randomized controlled trial (RCT) demonstrated superior 2-year overall survival (OS) of 85% in patients with resectable CRLM treated with HAIP and concurrent systemic chemotherapy (5-FU) compared to 69% in patients with resection and systemic chemotherapy (5-FU) only ($p = 0.02$).[10] A recent retrospective analysis evaluated 2368 consecutive patients undergoing complete resection of CRLM with and without adjuvant HAIP chemotherapy at MSKCC between 1992 and 2012.[11] The median OS with HAIP chemotherapy was 67 months versus 44 months without HAIP chemotherapy ($p < 0.001$). After adjusting for seven independent prognostic factors in multivariable analysis, the hazard ratio (HR) of HAIP chemotherapy was 0.67 (95% CI: 0.59-0.76, $p < 0.001$).[11] The median OS in the group without HAIP chemotherapy was similar to the 45 months found in a series of 2715 patients from the UK where no HAIP chemotherapy was used.[12] Subgroup analyses demonstrated that HAIP chemotherapy is particularly

effective in low-risk patients (median OS 89 months vs. 53 months, $p < 0.001$). In high-risk patients however, the difference in median OS was still statistically significant and clinically relevant, however, less pronounced (50 months vs. 37 months, $p < 0.001$).[13]

Methods/Design

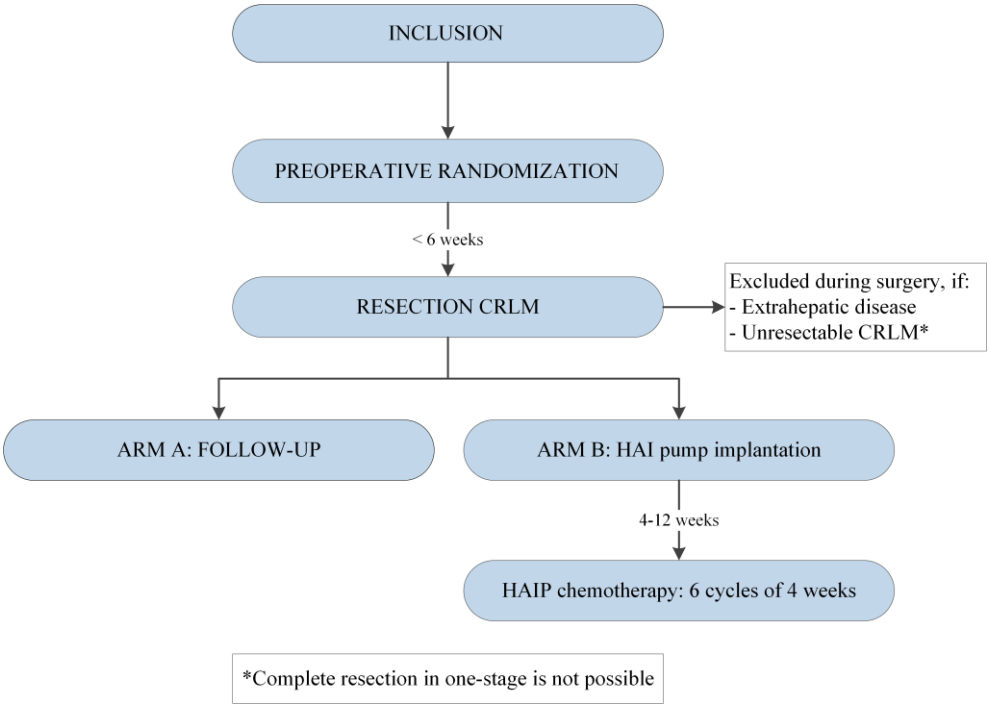
Objective

The primary aim is to compare the progression-free survival (PFS) of surgery with adjuvant HAIP chemotherapy to surgery alone in patients with resectable CRLM with a low CRS (CRS 0-2). Secondary objectives are to compare OS, postoperative complications, adverse events, quality of life, and costs between the two arms. Pharmacokinetics of intra-arterial administration of floxuridine will be investigated as well as predictive biomarkers for the efficacy of HAIP chemotherapy. In a side study, the accuracy of CT angiography will be compared to radionuclide scintigraphy to detect extrahepatic perfusion.

Study design

The PUMP trial is a phase III randomized controlled open label, multicenter trial to compare the combined efficacy of resection and/or open ablation and adjuvant HAIP chemotherapy to resection and/or open ablation alone in patients with CRC and resectable CRLM with a low CRS (0-2). This trial started in August 2018. Five centers participate in this study (Erasmus MC Cancer Institute, Rotterdam; Antoni van Leeuwenhoek, Amsterdam; Academic Medical Center, Amsterdam; University Medical Center Utrecht, Utrecht; IJsselland Hospital, Capelle aan den IJssel). Patients will be randomized in a 1:1 ratio (Figure 1) to resection of CRLM only (arm A), or resection of CRLM with adjuvant HAIP chemotherapy (arm B). Stratification factors will be center, number of CRLM (< 4 or ≥ 4 CRLM), and size of the largest CRLM (< 5cm or ≥ 5cm). Blinding is not feasible because of the nature of the intervention, including a visible subcutaneous pump. In patients who received preoperative chemotherapy for CRLM, the CRS values prior to start of preoperative chemotherapy should be used to determine eligibility. A computed tomography (CT) scan in (early) arterial phase of the liver is required prior to inclusion to determine whether intra-arterial catheter placement is technically possible. The multidisciplinary meeting should determine that complete resection of the CRLM is feasible. Resectability is defined as the opportunity to achieve an R0 resection with a sufficient liver remnant. Randomization will be performed preoperatively if the participant meets all the criteria.

Figure 1. Study flowchart



Study population

Adults with resectable CRLM without extrahepatic disease (EHD) and a low CRS (0-2) will be considered for inclusion.

Patients are eligible for this study when they meet the following inclusion criteria:

- age ≥ 18 years;
- eastern cooperative oncology group (ECOG) performance status 0 or 1;
- histologically confirmed CRC;
- radiologically confirmed CRLM, amenable for local treatment (resection or open ablation);
- CRS of 0-2. In patients with unknown nodal status of the CRC (in patients with synchronous resection of CRC and CRLM), the nodal status is counted as zero;
- positioning of a catheter for HAIP chemotherapy is technically feasible based on an early arterial phase CT angiography (CTA) (1 millimeter slide thickness);
- adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements to be conducted within 15 days prior to randomization: absolute neutrophil count (ANC) ≥1.5 x 109/L, platelets ≥ 100 x 109/L, hemoglobin (Hb) ≥ 5.5 mmol/L,

total bilirubin ≤ 1.5 upper normal limit (UNL), aspartate aminotransferase (ASAT) ≤ 5 x UNL, alanine aminotransferase (ALAT) ≤ 5 x UNL, alkaline phosphatase ≤ 5 x UNL, (calculated) glomerular filtration rate (GFR) >30 mL/min;
- written informed consent.

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

- presence of EHD, including positive portal lymph nodes, at the time of liver resection or any time since CRC diagnosis, with exception of small (≤ 1 cm) extrahepatic lesions which are not clearly suspicious of metastases (e.g., pulmonary lesions that are too small to characterize);
- second primary malignancy except in situ carcinoma of the cervix, adequately treated non-melanoma skin cancer, or other malignancy treated at least 5 years prior to inclusion without evidence of recurrence;
- prior hepatic radiation, resection, intra-arterial therapy or ablation;
- CRLM requiring two-staged liver resections;
- liver-first resections; but simultaneous resection of CRC and CRLM is not an exclusion criterion;
- (partial) portal vein thrombosis;
- known DPD-deficiency (heterozygous or homozygous of DPYP);
- 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;
- serious infections (uncontrolled or requiring treatment);
- participation in another interventional study for CRLM with survival as outcome;
- any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Treatment strategies

Standard procedures in control arm (arm A)
Patients included in the study should undergo surgery within 6 weeks after signing the informed consent. Local treatment (resection and/or open ablation) of the CRLM in both arms is in accordance with the national guidelines. An intra-operative ultrasound evaluation

of the liver will be performed to assure the feasibility of complete resection of the CRLM with an adequate liver remnant. Resection of CRLM can be performed either by minimal-invasive (laparoscopic or robotic) or open approach at the discretion of the surgeon.

Investigational procedures of the experimental arm (arm B)

The treatment of patients randomized to the experimental arm consists of HAI pump placement following complete resection and/or open ablation of all CRLM. Pump implantation will be cancelled in patients with unexpected unresectable CRLM or EHD detected at the time of surgery. Implantation of the HAI pump (Tricumed IP2000V infusion pump; Figure 2) is performed by an open or minimal-invasive approach. In patients requiring simultaneous resection of the primary tumor and CRLM, the colorectal resection is performed after pump placement to reduce the risk of pump contamination. The implantation procedure of the infusion pump and dose adjustment protocols have been discussed by previous authors and was optimized for the materials used in this trial.[14, 15] In addition to local treatment of the CRLM, a cholecystectomy is performed to avoid cholecystitis as a result of inadvertent intra-arterial chemotherapy of the gallbladder.[16] The pump catheter is positioned in the gastroduodenal artery (GDA) allowing perfusion of the entire liver without obstructing the flow in the hepatic artery. The pump catheter has rings at the distal end that allow for securing the catheter with non-absorbable ties in the GDA (Figure 3). 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.

Figure 2. Tricumed infusion pump

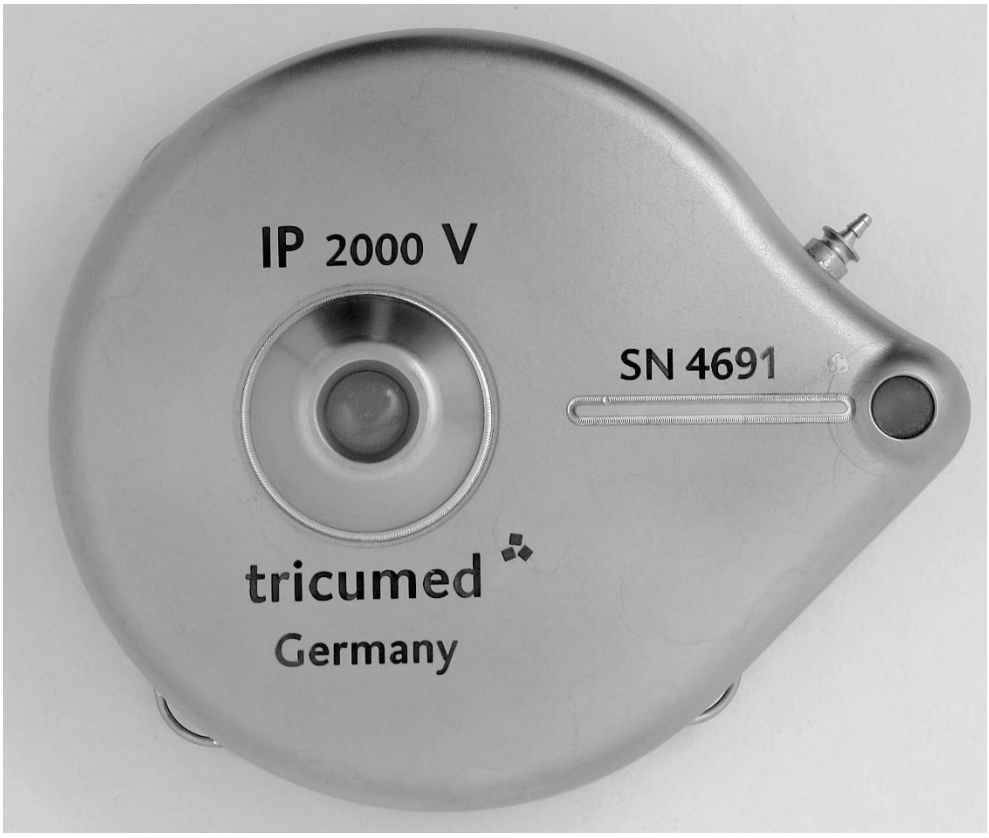


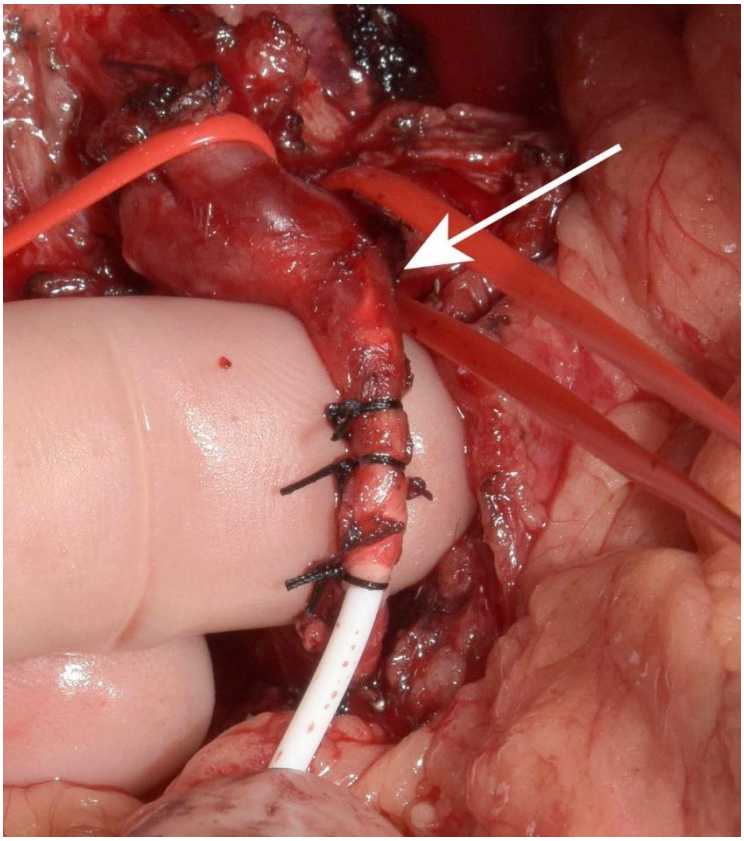
Figure 3. Distal tip of the intra-arterial catheter

The entire GDA and the proximal proper hepatic artery are mobilized and dissected circumferentially from their attachments to facilitate insertion of the catheter and to avoid inadvertent perfusion of the pancreas, stomach, or duodenum. Branches to the retroperitoneum arising from the right or left hepatic artery are common and should be ligated. The use of papaverine is optional to gain additional dilatation of the GDA.

Before implantation, a function test of the pump is performed to confirm flow. The pump pocket should be created in the left lower quadrant so that contact with the anterior superior iliac spine and the lower ribs is avoided. The pocket cavity should be 3/4 caudal to the incision to ensure an optimal position of the septum for refills. 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 catheter injury by a needle when accessing the pump percutaneously.

Next, the GDA is ligated with a nonabsorbable tie as far away (at least 2 cm) from the common hepatic artery as possible. 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 can be used alternatively to avoid occlusion of the hepatic artery. A transverse arteriotomy is made in the distal GDA, and the catheter is inserted up to but not beyond the junction with the hepatic artery (Figure 4). If the catheter protrudes into the common hepatic artery, turbulence of blood flow can lead to increased risk of thrombosis of the hepatic artery. 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, pseudo-aneurysm with bleeding, or late dislodgment. When positioned, the catheter should be secured with three to four nonabsorbable ties (silk 2.0) 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 methylene blue. After the perfusion test, the catheter is flushed with heparinized saline, and the wounds are closed.

Figure 4. Intra-arterial positioning securing of distal tip of the catheter



Arrow: Tip of the catheter is positioned at the orifice of the GDA

Postoperative procedures experimental arm

Prior to the first administration of intra-arterial chemotherapy, bilobar hepatic perfusion and lack of extrahepatic perfusion are confirmed by:

1. A multiphase or perfusion CT with contrast injection through the bolus port of the pump.
2. Technetium-99-labeled macroaggregated albumin (Tc-99m MAA) scintigraphy. Tc-99m MAA is administered through the pump bolus port. Within 1 hour after Tc-99M MAA injection, both planar imaging and a Single Photon Emission Computed Tomography (SPECT)/CT scan are performed.

Patients with extrahepatic perfusion are evaluated angiographically and aberrant branches embolized with re-testing prior to treatment.

Drug treatment plan experimental arm

The drug that is used for HAIP is floxuridine (also known as fluorodeoxyuridine (FUDR), Fresenius Kabi, LLC, USA). HAIP chemotherapy with floxuridine has been administered since the early eighties for patients with CRLM in the adjuvant, neo-adjuvant, and induction chemotherapy setting.[10, 16-24] 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. The pump reservoir is filled percutaneously with 0.12 mg/kg floxuridine together with 35.000 IE of heparin, 25 mg of dexamethasone, and enough normal saline for a total volume of 35 mL. 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, with a total of 6 cycles. On day 1, the pump reservoir is filled with floxuridine, dexamethasone, and heparinized saline. On day 15, the pump is emptied and refilled with heparinized saline (35.000 IE of heparin and enough normal saline for a total volume of 35 mL) for 2 weeks. Until completion of HAIP chemotherapy, patients will receive a prophylactic proton-pump inhibitor once daily. The use of NSAIDs is discouraged during HAIP treatment. Patients' complete blood counts and liver tests are monitored every 2 weeks during HAIP chemotherapy. In patients with abnormal liver values, dose reduction or discontinuation of HAIP chemotherapy is performed according to a predetermined protocol (Table 1). Dexamethasone (25 mg) is added to the heparinized saline in case of toxicity according to the values in Table 1 resulting in cessation of floxuridine.

Table 1. Dose adjustment schedule

	Reference Value (RV)* Upper limit of normal	% floxuridine 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 dose.

Follow-up

Follow-up for patients both randomized to arm A and arm B will be performed with CEA measurement and abdominal and chest CT including 4-phase liver imaging (year 1-3: every 3 months; year 4-5: every 6 months). The surgical complication score is measured two weeks and three months after surgery. The chemotherapy toxicity score is measured two weeks, three and six months after surgery. Quality of life is measured in both arms at baseline, every three months in the first year, and two and five years after surgery.

Study endpoints and analyses

Primary endpoint

Primary endpoint of this study will be PFS, calculated from the time between surgery and the first event defined as recurrence or death or last follow-up. Patients still alive without recurrence at last contact are censored.

Analysis of the primary endpoint

The formal test for difference in PFS between the two treatment arms will be done with a multivariable Cox regression analysis with adjustment for the stratification factor except hospital. The actuarial method of Kaplan and Meier will be used to estimate survival probabilities, while the Greenwood estimate will be used to construct corresponding 95% confidence intervals (CIs). Kaplan-Meier curves will be generated to illustrate PFS, for all patients as well as by treatment arm. A prespecified subgroup analysis will be performed for the following subgroups: node-negative CRC, CRS of 0 to 1 points, and KRAS wild-type.

Secondary endpoints

Secondary endpoints include: OS (calculated from surgery until death from any cause; patients still alive at last contact are censored), hepatic PFS, safety, quality of life (EQ-5D + QCQ-C30), and cost-effectiveness. Furthermore, the pharmacokinetic profile of intra-arterial

administration of floxuridine will be investigated in more detail. Moreover, we aim to identify predictive biomarkers (circulating tumor DNA) for the efficacy of HAIP chemotherapy. Finally, the accuracy of CT angiography will be evaluated compared to radionuclide scintigraphy to detect extrahepatic perfusion.

Sample size calculation

A median PFS of 17 months was observed in 228 low-risk patients with resectable CRLM at Erasmus MC treated between 2000 and 2012, without EHD (consistent with arm A). In a multivariable analysis using a consecutive cohort of 779 low-risk patients without EHD, treated with or without HAIP chemotherapy between 2000 and 2012 at MSKCC, a hazard ratio (HR) of 0.60 (95% CI: 0.49-0.75) was found. Given a HR of 0.60 (corresponding to a median PFS of 28 months in arm B), 80% power and a 2-sided significance level $\alpha = 0.05$, a total of 126 events need to be observed. With an expected accrual rate of 6 patients per month in five centers, 3 years accrual and one additional year of follow-up, and taking into account a drop-out rate of 5%, a total of 230 patients need to be randomized. No interim analysis is planned for survival outcomes.

Safety analysis

Interim analyses are performed for postoperative complications (grade 3 or higher) and adverse events (serious adverse events plus adverse events of grade 3 or higher) for early detection of unusually high rates of complications and adverse events in the experimental arm (arm B). Interim analyses are planned after inclusion of 20 and 50 patients in arm B.

Discussion

In this trial patients receive adjuvant HAIP chemotherapy without systemic chemotherapy. HAIP chemotherapy in MSKCC is always combined with concurrent adjuvant systemic chemotherapy. Adjuvant systemic chemotherapy is currently not recommended in Dutch guidelines for patients who underwent complete resection of CRLM, since no difference in OS was found in a large RCT.[3, 4] Some retrospective studies confirmed that adjuvant systemic chemotherapy has no impact on OS in patients with a low CRS.[25-27]

A previous RCT from MSKCC, which compared patients who received adjuvant systemic 5-fluorouracil (5-FU) and HAIP chemotherapy with patients who received systemic 5-FU alone demonstrated a beneficial 2-years OS of 85% with HAIP vs. 69% with 5-FU alone ($p = 0.02$).[10] Despite this result, HAIP chemotherapy has not been widely adopted. The National Comprehensive Cancer Network guidelines recommend adjuvant HAIP chemotherapy for CRLM as an option in experienced centers (Category 2B). A retrospective study from MSKCC demonstrated a superior OS of 23 months (67 months vs. 44 months) in patients treated with HAIP and concurrent systemic chemotherapy compared to systemic chemotherapy alone in patients with resectable CRLM. These results have renewed interest in HAIP chemotherapy outside MSKCC.[28] Another phase III RCT is required to compare adjuvant HAIP chemotherapy for CRLM with surgery alone. The PUMP trial aims to definitively elucidate the efficacy of adjuvant HAIP chemotherapy in patients with resectable CRLM.

Only low-risk patients without EHD will be eligible for inclusion in the PUMP trial. This subgroup demonstrated to benefit more (median OS 89 months vs. 53 months, $p < 0.001$) compared to high-risk patients (median OS 50 months vs. 35 months, $p < 0.001$). Furthermore, no survival benefit was found in patients with EHD prior to or at time of resection (median OS 37 months vs. 33 months, $p = 0.92$). These results have determined the study design and sample size calculation for the PUMP trial.

HAIP chemotherapy requires a well-trained large multidisciplinary team. A previous RCT investigating intra-arterial chemotherapy for CRLM, performed in 26 centers in Germany, was terminated early due to high complication rates.[29] Therefore, we comprehensively trained and proctored the five multidisciplinary teams participating in the PUMP trial. Moreover, a pilot study prior to the RCT has been conducted to confirm the safety and feasibility.

References

1. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; 224(4):509-20; discussion 520-2.
2. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
3. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371(9617):1007-16.
4. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-15.
5. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
6. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery* 1974; 75(4):589-96.
7. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954; 30(5):969-77.
8. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983; 10(2):176-82.
9. Dizon DS, Schwartz J, Kemeny N. Regional chemotherapy: a focus on hepatic artery infusion for colorectal cancer liver metastases. *Surg Oncol Clin N Am* 2008; 17(4):759-71, viii.
10. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.
11. Sadot E, Groot Koerkamp B, Leal JN, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? *Ann Surg* 2015; 262(3):476-85; discussion 483-5.
12. Hamady ZZ, Rees M, Welsh FK, et al. Fatty liver disease as a predictor of local recurrence following resection of colorectal liver metastases. *Br J Surg* 2013; 100(6):820-6.
13. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017:JCO2016718346.

14. Kingham TP, D'Angelica M, Kemeny NE. Role of intra-arterial hepatic chemotherapy in the treatment of colorectal cancer metastases. *J Surg Oncol* 2010; 102(8):988-95.
15. Ammori JB, Kemeny NE. Regional hepatic chemotherapies in treatment of colorectal cancer metastases to the liver. *Semin Oncol* 2010; 37(2):139-48.
16. Kemeny MM, Goldberg D, Beatty JD, et al. Results of a prospective randomized trial of continuous regional chemotherapy and hepatic resection as treatment of hepatic metastases from colorectal primaries. *Cancer* 1986; 57(3):492-8.
17. D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. *Ann Surg* 2015; 261(2):353-60.
18. Jarnagin WR, Schwartz LH, Gultekin DH, et al. Regional chemotherapy for unresectable primary liver cancer: results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. *Ann Oncol* 2009; 20(9):1589-95.
19. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy--an intergroup study. *J Clin Oncol* 2002; 20(6):1499-505.
20. Ammori JB, Kemeny NE, Fong Y, et al. Conversion to complete resection and/or ablation using hepatic artery infusional chemotherapy in patients with unresectable liver metastases from colorectal cancer: a decade of experience at a single institution. *Ann Surg Oncol* 2013; 20(9):2901-7.
21. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg* 2005; 201(1):57-65.
22. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
23. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2009; 27(21):3465-71.
24. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol* 2006; 24(9):1395-403.
25. Ayez N, van der Stok EP, Grunhagen DJ, et al. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol* 2015; 41(7):859-67.
26. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.

27. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg* 2012; 255(3):534-9.
28. NCCN Guidelines - Colon Cancer. 2015.
29. Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg* 1998; 228(6):756-62.

Part III

Prognostication and personalized treatment

Chapter 9

Histopathological growth patterns as biomarker for adjuvant systemic chemotherapy in patients with resected colorectal liver metastases

F.E. Buisman, E.P. van der Stok, B. Galjart, P.B. Vermeulen, V.P. Balachandran, R.R.J. Coebergh van den Braak, J.M. Creasy, D.J. Höppener, W.R. Jarnagin, T.P. Kingham, P.M.H. Nierop, E. Sadot, J. Shia, B. Groot Koerkamp, D.J. Grünhagen, M.I. 'Angelica, C. Verhoef

Clinical & Experimental Metastasis 2020; 37(5):593-605

Abstract

Background

Adjuvant systemic chemotherapy (CTx) is widely administered in patients with colorectal liver metastases (CRLM). Histopathological growth patterns (HGPs) are an independent prognostic factor for survival after complete resection. This study evaluates whether HGPs can predict the effectiveness of adjuvant CTx in patients with resected CRLM.

Methods

Two main types of HGPs can be distinguished; the desmoplastic type and the non-desmoplastic type. Uni- and multivariable analyses for overall survival (OS) and disease-free survival (DFS) were performed, in both patients treated with and without preoperative chemotherapy.

Results

A total of 1236 patients from two tertiary centers (Memorial Sloan Kettering Cancer Center, New York, USA; Erasmus MC Cancer Institute, Rotterdam, the Netherlands) were included (period 2000-2016). A total of 656 patients (53.1%) patients received preoperative chemotherapy. Adjuvant CTx was only associated with a superior OS in non-desmoplastic patients that had not been pretreated (adjusted hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.37-0.73, $p < 0.001$), and not in desmoplastic patients (adjusted HR 1.78, 95% CI 0.75-4.21, $p = 0.19$). In pretreated patients no significant effect of adjuvant CTx was observed, neither in the desmoplastic group (adjusted HR 0.83, 95% CI 0.49-1.42, $p = 0.50$) nor in the non-desmoplastic group (adjusted HR 0.96, 95% CI 0.71-1.29, $p = 0.79$). Similar results were found for DFS, with a superior DFS in non-desmoplastic patients treated with adjuvant CTx (HR 0.71, 95% CI 0.55-0.93, $p < 0.001$) that were not pretreated.

Conclusions

Adjuvant CTx seems to improve OS and DFS after resection of non-desmoplastic CRLM. However, this effect was only observed in patients that were not treated with chemotherapy.

Introduction

Pre- and or postoperative systemic chemotherapy is often administered in patients with potentially resectable colorectal liver metastases (CRLM). The effectiveness has been investigated in randomized controlled trials.[1-4] The long-term follow-up of a phase III trial demonstrated a superior early progression-free survival (PFS) for patients treated with perioperative FOLFOX. However, there was no difference in overall survival (OS) with long term follow-up.[5]

Retrospective studies have suggested that the effectiveness of systemic chemotherapy may depend on the extent of disease or factors associated with OS. Potentially positive associations of perioperative systemic chemotherapy and OS were seen in populations with a high clinical risk score (CRS), or elevated preoperative carcinoembryonic antigen (CEA) levels.[6-8] In order to adequately identify subgroups that benefit from adjuvant chemotherapy (CTx) after resection of CRLM, biomarkers that reflect actual tumor biology are needed.

Recent studies have suggested that the histopathological growth patterns (HGPs) of CRLM, obtained from hematoxylin and eosin (H&E) stained tissue sections after resection, are able to identify patients with an unfavorable tumor biology.[9-11] Two main types of HGPs can be distinguished; a desmoplastic type (dHGP) and a non-desmoplastic type (non-dHGP).[10, 12] The dHGP is driven by angiogenesis and elevated infiltration of immune cells is observed. Morphologically these tumors are characterized by a desmoplastic rim surrounding the tumor border. In non-dHGP CRLM, the tumor cells replace the liver parenchyma by using pre-existing liver vessels for blood supply (i.e., vessel co-option) instead of angiogenesis. [11, 12] Non-dHGP has been associated with a worse prognosis for patients undergoing resection of CRLM in multiple studies.[10, 13, 14] A large cohort study suggested that this effect was predominantly found in patients that were not pretreated with chemotherapy prior to CRLM resection.[10]

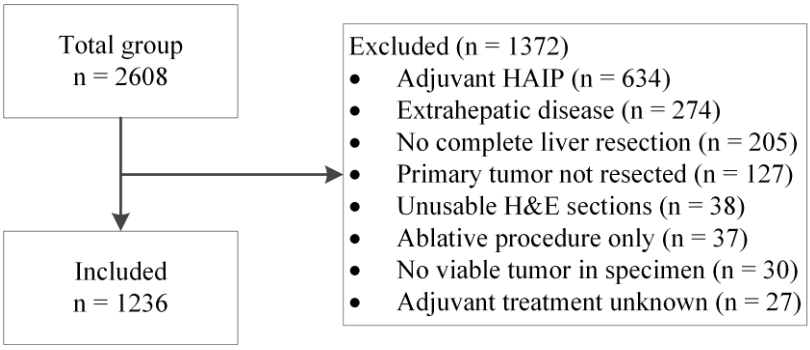
As HGPs reflect biological processes associated with tumor growth, this factor may be used to assess the effect of adjuvant CTx. This multicenter study aimed to evaluate if HGPs can be used to predict the effectiveness of adjuvant CTx after resection of CRLM.

Methods

Study population

All consecutive patients who underwent a complete resection of CRLM from 2000-2016 at Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA) and at the Erasmus MC Cancer Institute (Erasmus MC, Rotterdam, the Netherlands), were evaluated for inclusion. A total of 2608 consecutive patients were evaluated for inclusion. Patients were excluded from analysis for the following reasons: adjuvant hepatic artery infusion pump chemotherapy, R2 resection, no resection of primary tumor, extrahepatic disease prior to or at time of liver resection, and H&E stained tissue sections that were not suitable for scoring HGPs. H&E tissue sections were considered non-suitable if there was less than a 20% of the expected tumor-liver interface, showed poor tissue preservation or when viable tumor tissue was absent.[13] In total 1236 (47.4%) were eligible for inclusion (Figure 1).

Figure 1. Study flowchart



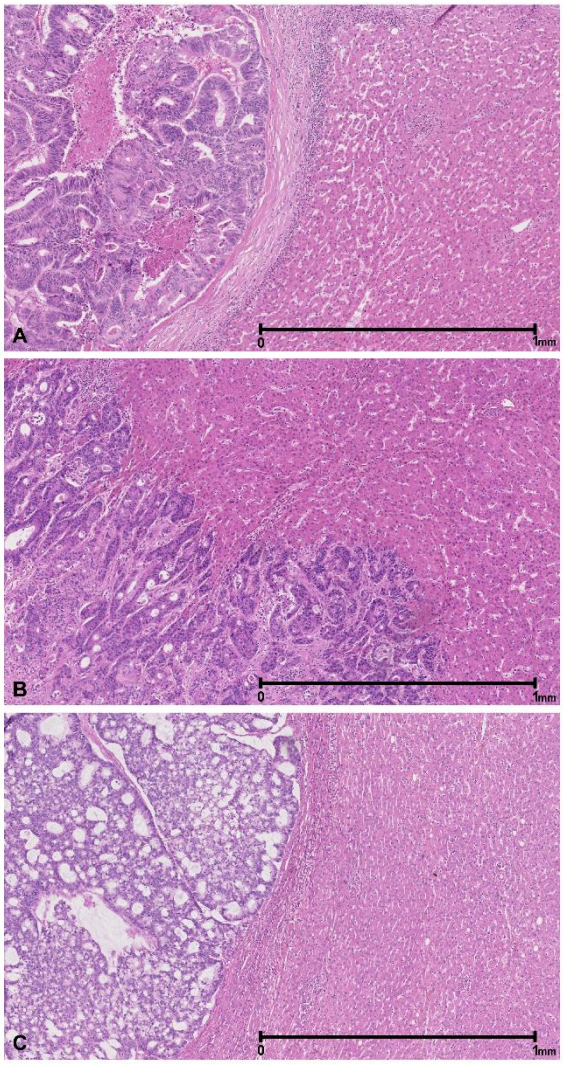
Abbreviations: HAIP: hepatic arterial infusion pump, H&E: hematoxylin and eosin

HGP characterization

HGPs were evaluated according to international guidelines.[13] In order to determine HGP type, all available H&E stained tissue sections off all available CRLM were evaluated using light microscopy for each patient. The entire interface between tumor and adjacent liver tissue was evaluated for the type of HGP and the proportion of each HGP was scored using percentages. Average HGP percentages were calculated per metastasis and per patient (in case of multiple CRLM). This method has been validated previously, demonstrating a 95% within CRLM concordance (in case of multiple H&E slides) and a 90% between metastases concordance (in case of multiple CRLM in one patient).[14] Patients were classified in two groups: dHGP if all available slides showed a 100% desmoplastic interface and non-dHGP if a replacement or pushing type HGP was found on one or more slides.[10] Non-dHGP CRLM represent a mix of different interfaces with a varying degree of desmoplastic, replacement,

and pushing type HGPs. Pushing type HGP CRLM are rare and are vascularized by angiogenensis in the absence of a desmoplastic stromal rim.[11, 12] (Figure 2)

Figure 2. H&E images of the HGP types



H&E tissue section. **a** desmoplastic HGP; **b** replacement HGP; **c** pushing HGP

Timing of chemotherapy

In MSKCC, most patients received pre- and/or postoperative (i.e., adjuvant) chemotherapy. In the Erasmus MC cohort, preoperative chemotherapy was regularly administered in referring hospitals or in patients with borderline resectable CRLM. Patients with upfront resectable CRLM were not treated with preoperative chemotherapy at Erasmus MC. Adjuvant chemotherapy is not the standard of care after resection of CRLM according to the Dutch guidelines. All analyses were performed separately for patients treated with and without preoperative chemotherapy according to the findings by Galjart et al, demonstrating limited prognostic value of HGPs in pretreated patients.[10]

Definitions

Clinicopathological data and postoperative treatment data were available from prospectively maintained databases. Synchronous CRLM were defined as detected within 3 months after resection of the primary tumor. Number and size of CRLM were derived from pathology reports. Any lesions treated with ablative therapies (radio frequency ablation or microwave ablation) were added to the total number of CRLM treated. The clinical risk score (CRS) was calculated by assigning one point for the presence of each of the five components: node positive primary tumor, disease-free interval between resection primary and diagnosis of CRLM less than 12 months, more than one CRLM, size of largest CRLM above 5 cm, and preoperative serum carcinoembryonic antigen (CEA) level of more than 200 μg/L.[8] The CRS was subdivided into low-risk (0-2 points) and high-risk (3-5 points). A positive resection margin was defined as the presence of viable tumor at the resection margin. Preoperative chemotherapy was defined as any chemotherapy administered within six months before liver resection. Adjuvant chemotherapy was defined as any systemic chemotherapy administered within six months after liver resection as long as it was not used for recurrent disease.

Statistical analysis

Differences between groups in baseline characteristics were evaluated using the Chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables. Median follow-up time for survivors was estimated using the reversed Kaplan-Meier method. Complete case analysis for the regression analyses was performed. Survival was estimated by the Kaplan-Meier method and groups were compared using the log-rank test. OS was defined from the date of CRLM resection until the date of last follow-up or death. Disease-free survival (DFS) was defined from the date of CRLM resection until the date of recurrence, last follow-up or death. Uni- and multivariable analyses of OS and DFS were performed with Cox proportional hazard modeling. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. Analyses were performed using SPSS (IBM Corp, version 24, Armonk, NY) and RStudio (RStudio, version 1.0.153, Boston, MA; survival package).

Results

Patient characteristics

A comparison at baseline was made between patients treated with and without adjuvant CTx (Table 1). Patients that were not pretreated who received adjuvant CTx had more common left-sided primary tumors (50.0% vs. 40.4%, $p < 0.001$). Patients that were pretreated who received adjuvant CTx had more advanced T-stage (pT3-4) primaries (91.5% vs. 84.6%, $p = 0.03$).

The median follow-up time for survivors was 83.0 months (IQR 51-118 months), and 720 patients (54.8%) died during follow-up. The 5-year OS for patients from MSKCC not treated with adjuvant CTx was 46.9% (95% CI 38.8%-56.7%) compared to 46.5% (95% CI 41.1%-52.6%) for patients from Erasmus MC ($p = 0.83$).

Overall survival and HGPs

Patients with dHGP had a 5-year OS of 63.4% (95% CI 57.7%-69.7%) compared to 45.9% (95% CI 42.6%-49.5%) in patients with non-dHGP ($p < 0.001$)(Supplementary Figure 1). In multivariable analysis, including the whole cohort, HGP was an independent predictor for OS (adjusted HR 1.57, 95% CI 1.29-1.92, $p = 0.008$) (Supplementary Table 1).

Adjuvant chemotherapy and HGPs in patients without pretreatment

Of all 1236 patients, 580 patients (46.9%) did not receive preoperative chemotherapy. Most of these patients originated from Erasmus MC (n = 377, 65.0%). Adjuvant CTx was administered in 129 patients (21.1%) of this subgroup. Five-year OS was 65.2% (95% CI 56.7%-74.9%) in patients treated with adjuvant CTx compared to 47.5% (95% CI 42.9%-52.6%) in patients not treated with adjuvant CTx ($p = 0.002$)(Figure 3a).

No difference in 5-year OS was observed in dHGP patients treated with adjuvant CTx compared to patients not treated with adjuvant CTx ($p = 0.17$)(Figure 3b). A 5-year OS (Figure 3c) of 64.9% (95% CI 55.8%-75.5%) was observed in non-dHGP patients treated with adjuvant CTx compared 40.3% (95% CI 35.3%-45.9%) in patients not treated with adjuvant CTx ($p < 0.001$). In multivariable analysis (Table 3) adjuvant systemic CTx was associated with a superior OS in non-dHGP patients (adjusted HR 0.52, 95% CI 0.37-0.72, $p < 0.001$), but not in dHGP patients (adjusted HR 1.78, 95% CI 0.75-4.21, $p = 0.19$)(Supplementary Table 2).

Table 1. Baseline characteristics

	Not pretreated				Pretreated			
	All patients	**No adjuvant CTx**	**Adjuvant CTx**		**All patients**	**No adjuvant CTx**	**Adjuvant CTx**	
	n (%)	*n (%)*	*n (%)*		*n (%)*	*n (%)*	*n (%)*	
Sample size	580 (100)	451 (77.8)	129 (21.2)	-	656 (100)	488 (74.4)	168 (25.6)	
Age (median, IQR)	66 (58-74)	66.0 (59-74)	66 (55-72)	0.84	62 (53-69)	63.0 (54-70)	58 (49-66)	0.05
Gender				0.08				0.27
Male	358 (61.7)	287 (63.6)	71 (55.0)		410 (62.5)	311 (63.7)	99 (58.9)	
Female	222 (38.3)	164 (36.4)	58 (45.0)		246 (37.5)	177 (36.3)	69 (41.1)	
Center				<0.001				<0.001
MSKCC	203 (35.0)	76 (16.9)	127 (98.4)		352 (53.7)	188 (38.5)	164 (97.6)	
Erasmus MC	377 (65.0)	375 (83.1)	2 (1.6)		304 (46.3)	300 (61.5)	4 (2.4)	
Colorectal cancer								
CRC location				<0.001				0.33
Right-sided	134 (23.8)	91 (20.8)	43 (3.7)		143 (22.5)	104 (21.7)	39 (25.0)	
Left-sided	239 (42.5)	177 (40.4)	62 (50.0)		305 (48.0)	227 (47.3)	305 (48.0)	
Rectum	189 (33.6)	170 (38.8)	19 (15.3)		188 (29.6)	149 (31.0)	188 (29.6)	
Missing	18				20			
pT-stage				0.27				0.03
T 0-2	106 (18.7)	87 (19.7)	19 (15.3)		82 (13.7)	69 (15.4)	13 (8.5)	
T 3-4	460 (81.3)	355 (80.3)	105 (84.7)		518 (86.3)	378 (84.6)	140 (91.5)	
Missing	14				56			

(Continued)	Not pretreated				Pretreated			
	All patients	**No adjuvant CTx**	**Adjuvant CTx**		**All patients**	**No adjuvant CTx**	**Adjuvant CTx**	
Nodal status CRC				0.86				0.98
N0	260 (4.54)	202 (45.3)	58 (4,57)		226 (35.2)	167 (35.0)	59 (35.8)	
N1	214 (37.3)	165 (37.0)	49 (38.6)		249 (38.8)	186 (39.0)	63 (38.2)	
N2	99 (17.3)	79 (17.7)	20 (15.7)		167 (26.0)	124 (26.0)	43 (26.1)	
Missing	7				14			
CRLM								
Disease free interval				0.27				0.85
≤ 12 months	301 (52.0)	240 (53.2)	67 (52.3)		547 (83.8)	408 (83.6)	139 (84.2)	
> 12 months	278 (48.0)	211 (46.8)	61 (47.7)		106 (16.2)	80 (16.4)	26 (15.8)	
Missing	1				3			
Number CRLM				0.58				0.18
1	334 (57.9)	257 (57.4)	77 (59.7)		208 (32.0)	156 (32.4)	52 (31.1)	
2	123 (21.3)	95 (21.2)	28 (21.7)		124 (19.1)	101 (21.0)	23 (13.8)	
3	68 (11.8)	55 (12.3)	13 (10.1)		87 (13.4)	66 (13.7)	21 (12.6)	
4	31 (5.4)	27 (6.0)	4 (3.1)		78 (12.0)	56 (11.6)	22 (13.2)	
5-9	17 (2.9)	11 (2.5)	6 (4.7)		134 (20.6)	92 (19.1)	42 (25.1)	
≥10	4 (0.7)	3 (0.7)	3 (0.7)		18 (2.8)	11 (2.3)	7 (4.2)	
Missing	2				3			

(Continued)	Not pretreated				Pretreated			
	All patients	**No adjuvant CTx**	**Adjuvant CTx**		**All patients**	**No adjuvant CTx**	**Adjuvant CTx**	
Size largest tumor				0.30				0.49
≤ 5cm	451 (80.0)	352 (80.9)	99 (76.6)		542 (84.0)	407 (84.7)	135 (82.3)	
> 5cm	113 (20.0)	83 (19.1)	30 (23.3)		103 (16.0)	74 (15.4)	29 (17.7)	
Missing	16				11			
Preoperative CEA				0.81				0.84
≤ 200 µg/L	521 (94.6)	409 (94.7)	112 (94.1)		546 (89.8)	403 (90.0)	143 (89.4)	
> 200 µg/L	30 (5.4)	23 (5.3)	7 (5.9)		62 (10.2)	45 (10.0)	17 (10.6)	
Missing	29				48			
Clinical risk score				0.44				0.93
0-2	429 (76.1)	333 (75.3)	96 (78.7)		311 (50.0)	230 (49.9)	81 (50.3)	
3-5	135 (23.9)	109 (24.7)	26 (21.3)		311 (50.0)	231 (50.1)	80 (49.7)	
Missing	16				34			
Resection margin involved				0.50				0.47
Yes	69 (11.9)	60 (13.4)	9 (7.0)		118 (18.0)	91 (18.7)	27 (16.2)	
No	509 (88.1)	389 (86.6)	120 (93.0)		536 (82.0)	396 (81.3)	140 (83.8)	
Tumor ablation at time of resection				0.54				0.85
Yes	48 (8.3)	39 (8.6)	9 (7.0)		204 (31.1)	153 (31.4)	51 (30.5)	
No	532 (91.7)	412 (91.4)	120 (93.0)		451 (68.9)	335 (68.6)	116 (69.5)	
Missing	0				1			

(Continued)	Not pretreated				Pretreated			
	All patients	**No adjuvant CTx**	**Adjuvant CTx**		**All patients**	**No adjuvant CTx**	**Adjuvant CTx**	
CTx regimen (pre/postoperative)				<0.001				0.28
Oxaliplatin / irinotecan based	83 (15.2)	0	83 (85.6)		581 (97.6)	159 (98.8)	422 (97.2)	
5-FU based	14 (2.6)	0	14 (14.4)		14 (2.4)	2 (1.2)	12 (2.8)	
No CTx	450 (82.3)	450 (100)	0					
Missing	33				61			
HGP				0.15				0.75
dHGP	91 (15.7)	76 (16.9)	15 (11.6)		189 (28.8)	349 (71.5)	50 (29.8)	
non-dHGP	489 (84.3)	375 (83.1)	114 (88.4)		467 (71.2)	139 (28.5)	118 (70.2)	

Abbreviations: Erasmus MC: Erasmus Medical Center, CEA: carcinoembryonic antigen, cm: centimeter, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, dHGP: desmoplastic type histopathological growth pattern, HGP: histopathological growth pattern, IQR: inter quartile range, MSKCC: Memorial Sloan Kettering Cancer Center, non-dHGP: non-desmoplastic type histopathological growth pattern, pT-stage: tumor-stage derived from pathology report.

Table 2. Uni- and multivariable Cox regression analysis for overall survival in non-dHGP patients (not pretreated)

	Univariable			Multivariable		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
Age at resection	1.02	1.01-1.03	0.006	1.02	1.01-1.03	0.006
Right-sided primary tumor	1.27	0.97-1.66	0.08	1.36	1.03-1.80	0.03
Clinical risk score (3-5)	1.72	1.34-2.23	<0.001	1.85	1.43-2.41	<0.001
R1 resection	1.37	1.00-1.88	0.05	1.21	0.86-1.70	0.28
Adjuvant CTx	0.53	0.39-0.73	<0.001	0.52	0.37-0.73	<0.001

Abbreviations: CI: confidence interval, CTx: chemotherapy, non-dHGP: non-desmoplastic type histopathological growth pattern, HR: hazard ratio, R1 resection: positive resection margin

Adjuvant systemic chemotherapy and HGPs in patients with pretreatment

A total of 656 patients (53.1%) patients received preoperative chemotherapy, of which 352 originated from MSKCC (53.7%). Adjuvant CTx was administered in 168 patients (25.6%) of patients who were pretreated prior to surgery. Five-year OS was 52.2% (95% CI 44.4%-61.3%) in patients treated with adjuvant CTx compared to 47.6% (95% CI 43.1%-52.7%) in patients not treated with adjuvant CTx ($p = 0.15$) (Figure 3d).

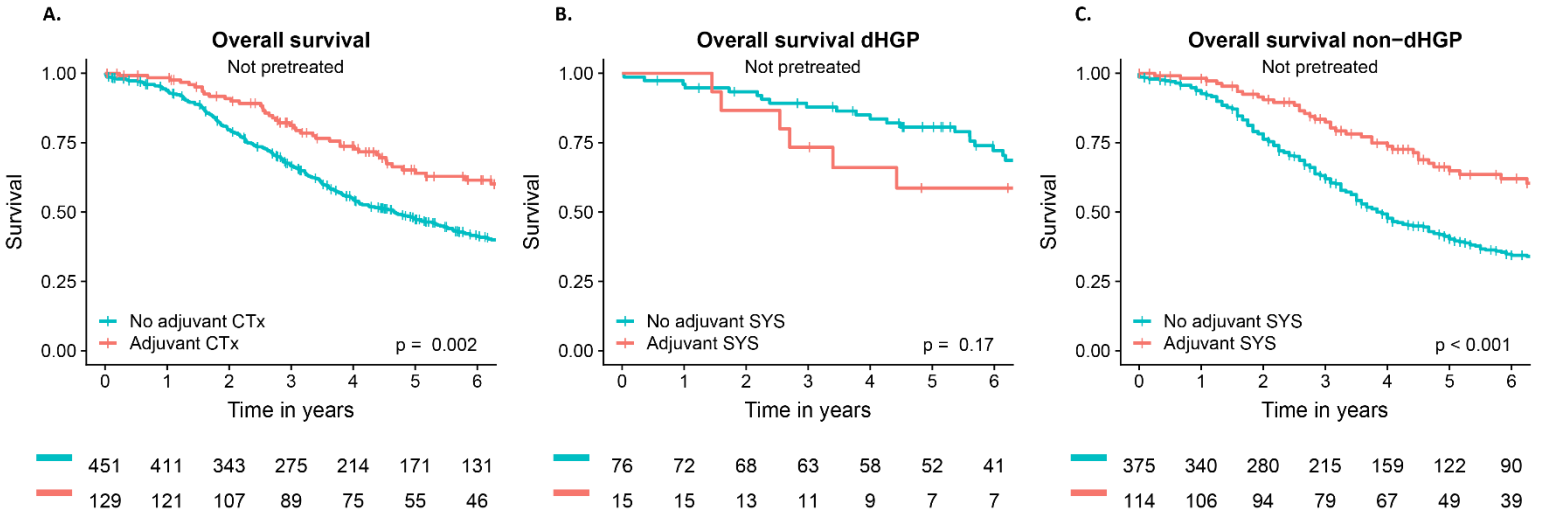
No difference in 5-year OS was observed in dHGP and non-dHGP patients treated with adjuvant CTx compared to patients not treated with adjuvant CTx ($p = 0.50$ and $p = 0.19$)(Figure 3e and 3f). In multivariable analysis adjuvant CTx was not associated with OS in dHGP patients (adjusted HR 0.83, 95% CI 0.49-1.42, $p = 0.50$), nor in non-dHGP patients (adjusted HR 0.96, 95% CI 0.71-1.29, $p = 0.79$)(Supplementary Table 3).

Disease-free survival and HGPs

A superior 5-year DFS of 35.7% was found for patients with a dHGP compared to 18.7% in patients with a non-dHGP ($p < 0.001$). HGP was an independent factor for DFS in multivariable analysis (adjusted HR non-dHGP 1.52, 95% CI 1.28-1.80, $p < 0.001$)(Supplementary Table 4).

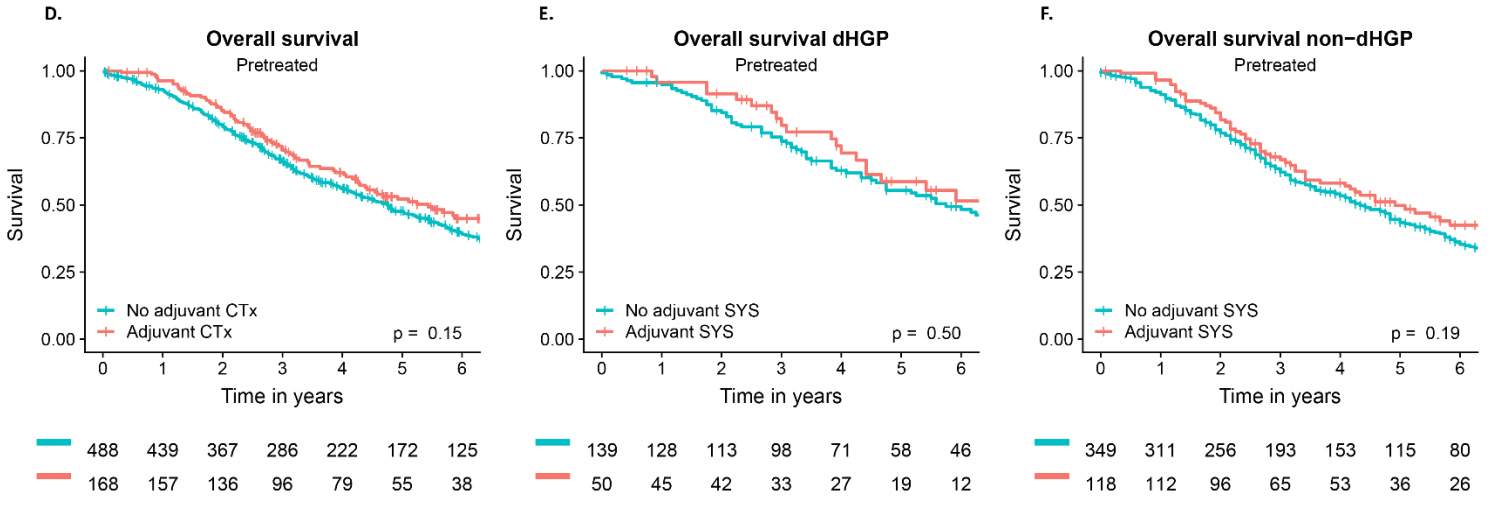
Superior 5-year DFS with adjuvant systemic treatment was only observed in patients with a non-dHGP that were not pretreated (20.4% vs. 10.1%, $p < 0.001$)(Supplementary Figure 2C). This was confirmed in multivariable analysis (adjusted HR 0.71, 95% CI 0.55-0.93, $p < 0.001$)(Supplementary Table 5 and 6).

Figure 3a-c. Kaplan-Meier of overall survival



Patients treated with adjuvant CTx were compared to patients not treated with adjuvant CTx in the population of patients that were not pretreated (a-c). The following populations were evaluated: (a) total patient cohort not pretreated, (b) dHGP patients not pretreated, and (c) non-dHGP patients not pretreated.

Figure 3d-f. Kaplan-Meier of overall survival



Furthermore, patients treated with adjuvant CTx were compared to patients not treated with adjuvant CTx in the population of patients that were pretreated (d-f). The following populations were evaluated: (d) total patient cohort pretreated, (e) dHGP patients pretreated, and (f) non-dHGP patients pretreated.

Discussion

This study investigates whether histopathological growth patterns predict the effect of adjuvant systemic chemotherapy after resection of CRLM. The results suggest that HGPs, that are assessed after resection of CRLM, are associated with the effectiveness of adjuvant CTx. Adjuvant CTx seemed highly effective in non-dHGP patients that were not pretreated with chemotherapy, resulting in improved OS (adjusted HR 0.52, $p < 0.001$) and DFS (adjusted HR 0.71, $p < 0.001$). In dHGP patients and in non-dHGP patients pretreated with CTx, no beneficial effect of adjuvant CTx could be demonstrated. Thereby, this study suggests that HGPs can be used to select patients for adjuvant CTx.

In order to determine the effectiveness of perioperative chemotherapy, several studies have been performed.[1-5] A large randomized trial evaluated the effectiveness of perioperative FOLFOX in patients with resectable CRLM (EORTC 40983).[1] Although this study was not powered on OS, and OS was not the primary endpoint of the study, no significant OS benefit was found after long-term follow-up.[5] Several non-randomized studies found that subgroups of patients may benefit from additional treatment with chemotherapy. These studies suggest that (neo-)adjuvant systemic chemotherapy might improve OS in patients at high risk of recurrence (i.e., aggressive tumor biology).[6, 7] Post hoc analysis of the EORTC 40983 trial demonstrated beneficial progression free survival in patients with elevated preoperative CEA levels (>5 ng/mL).[15] Furthermore, multiple previous studies have shown that the survival of patients with non-dHGP tumors is worse.[11, 12, 16, 17] Also, non-dHGP (and especially the replacement-type of growth) is associated with several aggressive biological characteristics such as high histological grade, lack of inflammation, and increased cancer cell motility.[11, 12, 16, 17] Therefore, the observed higher effectiveness of adjuvant CTx in patients with non-dHGP, i.e., more aggressive tumors, is in line with previous research, although validation of these findings is needed. Biological explanations of why only patients with non-dHGP appear to benefit from adjuvant CTx are lacking.

A previous study suggests that the HGPs are a strong prognostic factor in patients who are not pretreated, and in pretreated patients the prognostic value was less.[10] This observation led to the analyses of the current study. In pretreated patients HGP was not suitable to identify patients that benefit from adjuvant CTx. Previously we observed a higher proportion of dHGP (30% vs 19%, $p < 0.001$) after preoperative chemotherapy, suggesting a potential conversion to dHGP after pretreatment.[10] All in all, we believe that preoperative chemotherapy importantly changes HGPs. This could very well explain why the effect of HGPs on the effectiveness of adjuvant chemotherapy could only be demonstrated in those who were not pre-treated with chemotherapy.

Remarkably, we found that adjuvant CTx was not beneficial at all in pretreated patients. This observation was independent for the HGP type. Similar observations were reported in previous studies, suggesting that pre- and postoperative chemotherapy is not superior to pre-

or postoperative chemotherapy alone.[18, 19] Explanations for this observation remain hypothetical, especially in the field of metastasized colorectal cancer. In colorectal cancer, it has been suggested that adjuvant chemotherapeutical regimes of only 3 months are as effective as 6 months.[20] This may also have been the case in the current study. Unfortunately, we could confirm this hypothesis since the number of cycles administered was unknown.

One could hypothesize that preoperative chemotherapy may be able to eliminate (extra)hepatic micrometastases. In that case, additional chemotherapy after surgery might be unnecessary. In patients that were not pretreated, additional postoperative chemotherapy may be able to eliminate the remaining micrometastatic disease. After all, it seems that timing of chemotherapy is not crucial. Chemotherapy administered at any time pre- or postoperative may be beneficial in patients with upfront resectable CRLM.

However, adjuvant administration of chemotherapy in patients with upfront resectable CRLM may have several practical advantages compared to preoperative administration of chemotherapy. First, the normal liver parenchyma is not affected by chemotherapy prior to surgery, thereby not affecting the regenerative ability of the liver after resection. Also, the HGP can be assessed unambiguously after surgery, without the toxic effects on tumor cells and normal liver parenchyma. Adjuvant chemotherapy may also adhere to expectations of patients that prefer upfront surgery without postponement surgery by preoperative chemotherapy.

It should be noticed that the cohort of the current study comprised of initially borderline and upfront resectable CRLM that were treated with preoperative chemotherapy. In case of borderline resectable CRLM, administration of preoperative chemotherapy is obvious.

The results of this study should be interpreted in the light of several limitations. Most importantly, the non-randomized retrospective nature of this study. Some unidentified factors may have accounted for an unknown heterogeneity among the groups. In addition, the majority of patients treated with adjuvant CTx originated from MSKCC (over 95% in both groups). In the Erasmus MC Cancer Institute, no standard adjuvant CTx is given, according to the national guidelines. However, as discussed, no major significant differences were found at baseline. Furthermore, 5-year OS in patients not treated with adjuvant CTx from MSKCC and Erasmus MC was not statistically significant (49.1% vs. 46.4%, $p = 0.65$), supporting that there are no differences in patient-outcome at baseline. Another factor that could have introduced unaccounted bias is the fact that in some patients resection was combined with ablation of one or more lesions. In some patients the HGP type could be misinterpreted, however this is probably limited since our previous study demonstrated a very high concordance of > 90% between metastases (in case of multiple CRLM in one patient).[14]

This is the first study that demonstrates the predictive value of HGPs for adjuvant CTx after resection of CRLM. HGPs are an easily available, affordable and reliable method for clinicians to gather additional information. Other studies are needed to confirm our findings. Moreover, randomized controlled trials investigating the effectiveness of adjuvant CTx might consider HGPs as a stratification factor in the analysis.

In conclusion, the current study suggests that HGPs are associated with the effectiveness of adjuvant CTx after resection of CRLM. Patients with non-dHGP seem more likely to benefit from adjuvant CTx, while patients with dHGP do not. After pre-operative chemotherapy, adjuvant chemotherapy seems of no further benefit, irrespective of HGP. Clinicians may consider both the HGP and prior chemotherapy as factors to guide the decision for adjuvant CTx after resection of CRLM.

References

1. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371(9617):1007-16.
2. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; 15(6):601-11.
3. Ychou M, Hohenberger W, Thezenas S, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. *Ann Oncol* 2009; 20(12):1964-70.
4. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; 26(30):4906-11.
5. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-15.
6. Ayez N, van der Stok EP, Grunhagen DJ, et al. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol* 2015; 41(7):859-67.
7. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.
8. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
9. Nierop PMH, Galjart B, Hoppener DJ, et al. Salvage treatment for recurrences after first resection of colorectal liver metastases: the impact of histopathological growth patterns. *Clin Exp Metastasis* 2019; 36(2):109-118.
10. Galjart B, Nierop PMH, van der Stok EP, et al. Angiogenic desmoplastic histopathological growth pattern as a prognostic marker of good outcome in patients with colorectal liver metastases. *Angiogenesis* 2019.
11. Frentzas S, Simoneau E, Bridgeman VL, et al. Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat Med* 2016; 22(11):1294-1302.
12. Vermeulen PB, Colpaert C, Salgado R, et al. Liver metastases from colorectal adenocarcinomas grow in three patterns with different angiogenesis and desmoplasia. *J Pathol* 2001; 195(3):336-42.

13. van Dam PJ, van der Stok EP, Teuwen LA, et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 2017.
14. Hoppener DJ, Nierop PMH, Herpel E, et al. Histopathological growth patterns of colorectal liver metastasis exhibit little heterogeneity and can be determined with a high diagnostic accuracy. *Clin Exp Metastasis* 2019; 36(4):311-319.
15. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg* 2012; 255(3):534-9.
16. van Dam PJ, Daelemans S, Ross E, et al. Histopathological growth patterns as a candidate biomarker for immunomodulatory therapy. *Semin Cancer Biol* 2018; 52(Pt 2):86-93.
17. Stessels F, Van den Eynden G, Van der Auwera I, et al. Breast adenocarcinoma liver metastases, in contrast to colorectal cancer liver metastases, display a non-angiogenic growth pattern that preserves the stroma and lacks hypoxia. *Br J Cancer* 2004; 90(7):1429-36.
18. Allard MA, Nishioka Y, Beghdadi N, et al. Multicentre study of perioperative versus adjuvant chemotherapy for resectable colorectal liver metastases. *BJS Open* 2019; 3(5):678-686.
19. Araujo R, Gonen M, Allen P, et al. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. *Ann Surg Oncol* 2013; 20(13):4312-21.
20. Grothey A, Sobrero AF, Shields AF, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. *N Engl J Med* 2018; 378(13):1177-1188.

Supplementary Table 1. Uni- and multivariable Cox regression analysis for overall survival

	Univariable			Multivariable		
Covariate	HR	95% CI	p-value	HR	95% CI	P-value
Age at resection	1.02	1.01-1.02	<0.001	1.02	1.01-1.03	<0.001
Right-sided primary tumor	1.33	1.12-1.59	0.001	1.27	1.06-1.52	0.01
Clinical risk score (3-5)	1.59	1.37-1.85	<0.001	1.64	1.39-1.93	<0.001
R1 resection	1.48	1.22-1.79	<0.001	1.32	1.07-1.62	0.008
Preoperative CTx	1.11	0.96-1.28	0.17	1.12	0.95-1.32	0.17
Adjuvant CTx	1.35	1.12-1.62	0.002	0.77	0.63-0.93	<0.001
Non-dHGP	1.54	1.28-1.86	<0.001	1.57	1.29-1.92	0.008

Abbreviations: CI: confidence interval, CTx: chemotherapy, non-dHGP: non-desmoplastic type histopathological growth pattern, HR: hazard ratio, R1 resection: positive resection margin

Supplementary Table 2. Uni- and multivariable Cox regression analysis for overall survival in dHGP patients (not pretreated)

	Univariable			Multivariable		
Covariate	HR	95% CI	p-value	HR	95% CI	P-value
Age at resection	1.06	1.03-1.10	<0.001	1.04	1.00-1.08	0.03
Right-sided CRC	4.35	2.17-8.74	<0.001	3.93	1.67-9.27	0.002
Clinical risk score (3-5)	2.42	1.13-5.18	0.02	4.01	1.72-9.37	0.001
R1 resection	1.56	0.47-5.12	0.47	2.23	0.50-9.95	0.29
Adjuvant CTx	1.66	0.78-3.57	0.19	1.78	0.75-4.21	0.19

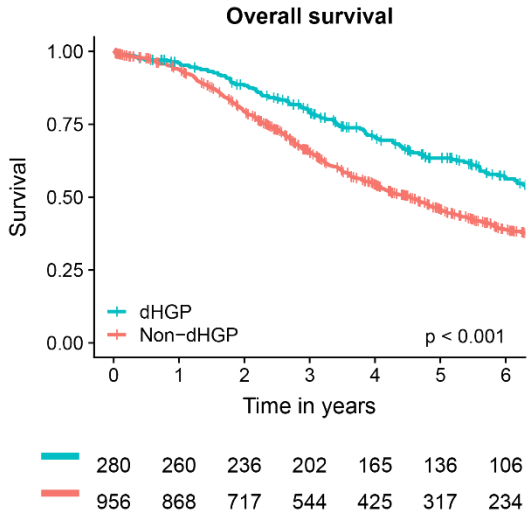
Abbreviations: CI: confidence interval, CTx: chemotherapy, dHGP: desmoplastic type histopathological growth pattern, HR: hazard ratio, R1 resection: positive resection margin

Supplementary Table 3. Uni- and multivariable Cox regression analysis for overall survival in dHGP and non-dHGP patients (pretreated)

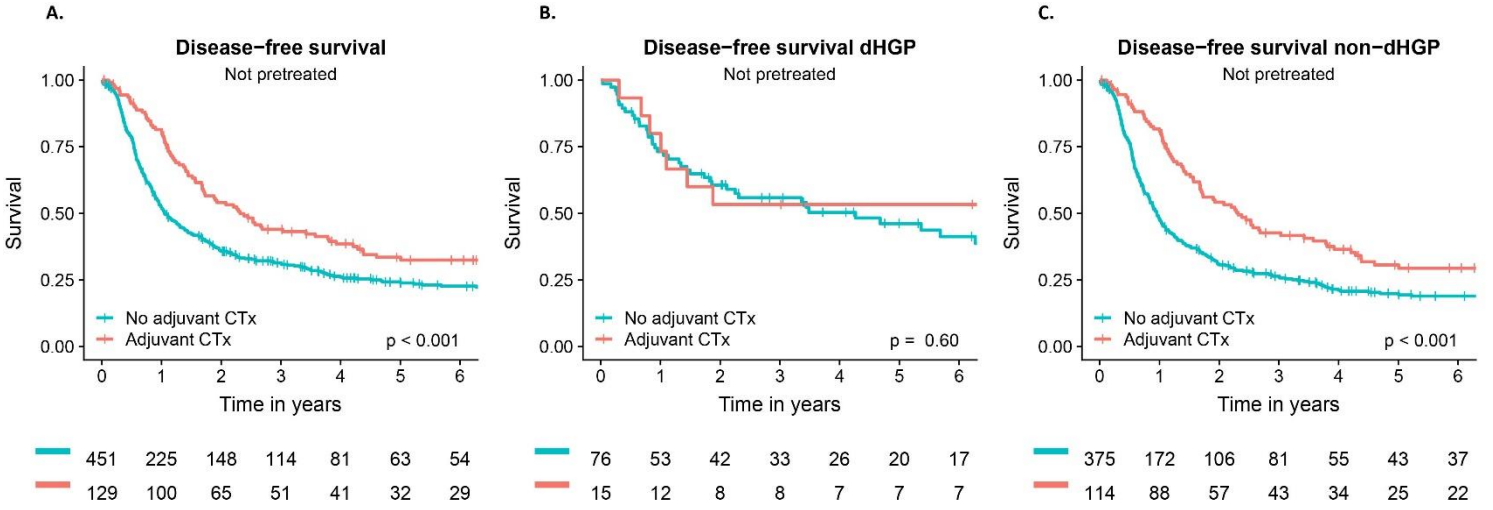
dHGP	Univariable			Multivariable		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
Age at resection	1.01	0.99-1.03	0.19	1.02	1.00-1.04	0.10
Right-sided CRC	1.21	0.73-1.99	0.46	1.17	0.70-1.95	0.56
Clinical risk score (3-5)	1.22	0.80-1.86	0.35	1.39	0.89-2.16	0.15
R1 resection	1.15	0.64-2.07	0.64	1.21	0.65-2.25	0.54
Adjuvant CTx	0.85	0.52-1.38	0.50	0.83	0.49-1.42	0.50
Non-dHGP	Univariable			Multivariable		
Covariate	HR	95% CI	P-value	HR	95% CI	P-value
Age at resection	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	0.003
Right-sided CRC	1.96	0.90-1.58	0.22	1.09	0.82-1.47	0.55
Clinical risk score (3-5)	1.53	1.21-1.95	<0.001	1.48	1.16-1.89	0.002
R1 resection	1.48	1.13-1.94	0.005	1.38	1.04-1.85	0.03
Adjuvant CTx	0.83	0.63-1.10	0.19	0.96	0.71-1.29	0.79

Abbreviations: CI: confidence interval, CTx: chemotherapy, dHGP: desmoplastic type histopathological growth pattern, non-dHGP: non-desmoplastic type histopathological growth pattern, HR: hazard ratio, R1 resection: positive resection margin

Supplementary Figure 1. Kaplan-Meier of overall survival stratified by HGP

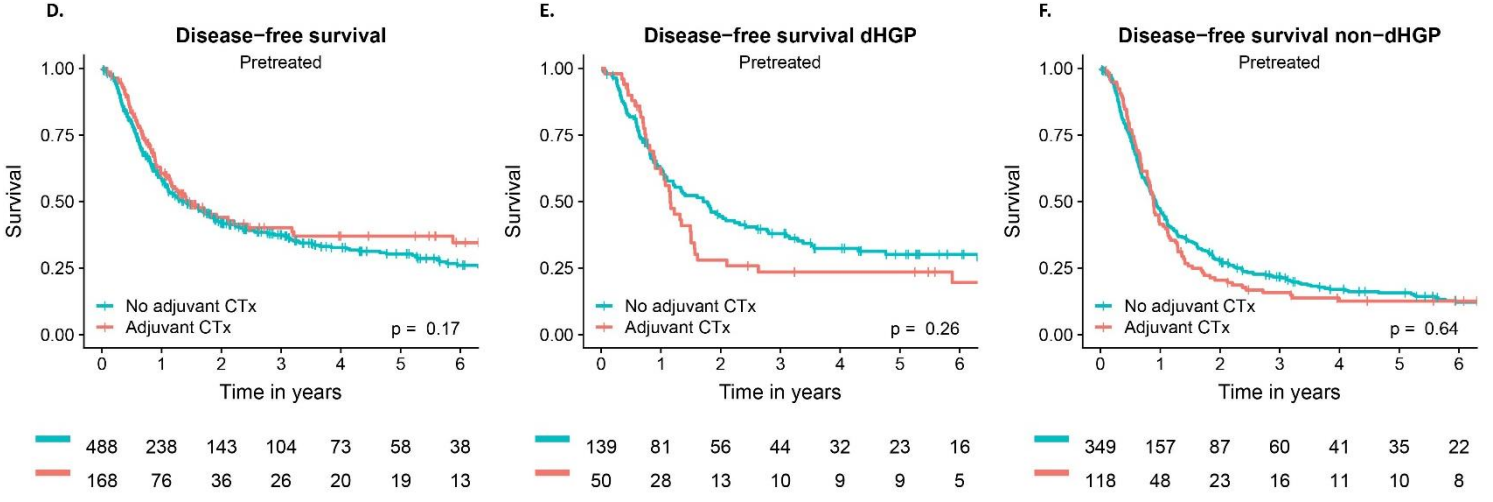


Supplementary Figure 2d-f. Kaplan-Meier of disease-free survival



Patients treated with adjuvant CTx were compared to patients not treated with adjuvant CTx in the population of patients that were not pretreated (a-c). The following populations were evaluated: (a) total patient cohort not pretreated, (b) dHGP patients not pretreated, and (c) non-dHGP patients not pretreated.

Supplementary Figure 2a-c. Kaplan-Meier of disease-free survival



Furthermore, patients treated with adjuvant CTx were compared to patients not treated with adjuvant CTx in the population of patients that were pretreated (d-f). The following populations were evaluated: (d) total patient cohort pretreated, (e) dHGP patients pretreated, and (f) non-dHGP patients pretreated.

Chapter 10

Predicting 10-year survival after resection of colorectal liver metastases; an international study including biomarkers and perioperative treatment

F.E. Buisman, D. Giardiello, N.E. Kemeny, E.W. Steyerberg, D.J. Höppener, B. Galjart, P.M.H. Nierop, V.P. Balachandran, A. Cercek, J.A. Drebin, M. Gönen, W.R. Jarnagin, T.P. Kingham, P.B. Vermeulen, A.C. Wei, D.J. Grünhagen, C. Verhoef, M.I. D'Angelica*, B. Groot Koerkamp*

*Shared senior authors

Under review European Journal of Cancer

Abstract

Background

Several patient and tumor characteristics are known poor prognostic factors. The aim of this study was to develop a prediction model for 10-year overall survival (OS) after resection of colorectal liver metastasis (CRLM) based on patient, tumor, and treatment characteristics.

Methods

Consecutive patients after complete resection of CRLM were included from two centers (1992-2019). A prediction model providing 10-year OS probabilities was developed using Cox regression analysis including genetic and pathological biomarkers (i.e., KRAS, BRAF, and histopathological growth patterns). Discrimination and calibration were assessed using cross-validation. A web-based calculator was built for individual 10-year OS probabilities.

Results

A total of 4112 patients were included. During a median follow-up of 8 years (25-75 percentile: 5-12) 2372 (58%) died. At 10-years follow-up, 510 (21%) patients were alive of whom 9 (2%) developed a recurrence after 10-years. The estimated 10-year OS was 30% (95% CI 29-32). Fifteen patient, tumor and treatment characteristics were independent prognostic factors for 10-year OS (age, gender, location and nodal status of the primary tumor, disease-free interval, number and diameter of CRLM, preoperative CEA, resection margin, extrahepatic disease, KRAS and BRAF mutation status, histopathological growth patterns, perioperative systemic chemotherapy and hepatic arterial infusion pump chemotherapy). The discrimination at 10-years was 0.73 in each center. A simplified risk score identified four risk groups with a 10-year OS of 57%, 38%, 24%, and 12%, respectively.

Conclusions

Ten-year OS after resection of CRLM is best predicted with a model including 15 patient, tumor, and treatment characteristics. The web-based calculator can be used to inform patients. This model serves as a benchmark to determine the prognostic value of novel biomarkers.

Introduction

Survival beyond 10-years after resection of colorectal liver metastases (CRLM) reflects cure in most (98%) patients.(1, 2) While most recurrences occur within the first two years after resection, patients continue to be at risk for recurrence in subsequent years.[1] Five-year overall survival (OS) is typically reported in randomized controlled trials (RCTs) and series, but does not reflect cure. Most studies found a 5-year survival of roughly 50% and a 10-year survival of 25% after resection of CRLM. Estimates of 10-year OS, however, vary across a wide range due to small sample size and limited follow-up of most studies.[2-7]

Moreover, the probability of 10-year OS varies widely across individual patients after resection of CRLM. Known unfavorable prognostic factors associated with 10-year survival include node-positive primary colorectal cancer (CRC), right-sided CRC, synchronous presentation, multiple metastases, CRLM large in size, high serum carcinoembryonic antigen (CEA) levels, presence of extrahepatic disease, and positive resection margins. However, no single unfavorable factor precludes 10-year OS.[1, 2] Other biomarkers (e.g., KRAS, BRAF, and histological growth pattern (HGP)) have been introduced to further improve prognostication after resection of CRLM. These biomarkers have been included in models to predict 5-year OS, but sample size and follow-up were inadequate for consideration of all known factors and for 10-year OS.[8-10]

Several RCTs have investigated the impact of perioperative chemotherapy on survival, including systemic chemotherapy and hepatic arterial infusion pump (HAIP) chemotherapy.[11-16] Although long-term survival outcomes of these treatments have been published [17, 18], these treatment factors have yet to be incorporated in prediction models.

The aim of this study was to develop a prediction model for 10-years OS for individual patients with resected CRLM based on patient, tumor, and treatment characteristics.

Methods

This study was performed according to the TRIPOD guidelines for transparent reporting of a multivariable prediction model for individual prognosis or diagnosis.[19]

Patients

Consecutive patients who underwent resection of CRLM between January 1992 and January 2019 from Memorial Sloan Kettering Cancer Center (MSKCC; New York, USA) and between January 2000 and January 2019 from Erasmus MC Cancer Institute (Rotterdam, the Netherlands) were included. Patients were also included if some or all CRLM were ablated rather than resected.

Perioperative management

Preoperative systemic chemotherapy was administered in patients with borderline resectable or unresectable CRLM for downstaging in both centers. Neoadjuvant systemic chemotherapy (i.e., for resectable CRLM) and adjuvant systemic chemotherapy were administered at MSKCC at the discretion of the treating physicians. Perioperative systemic chemotherapy for resectable tumors was rarely given at Erasmus MC, in accordance with Dutch national guidelines.[20] Systemic chemotherapy regimens changed over time and varied due to changing protocols and physicians' discretion. Moreover, some patients were treated with perioperative (preoperative downstaging and/or adjuvant) HAIP chemotherapy with floxuridine, mostly in addition to systemic chemotherapy.[21, 22]

Definitions

The primary CRC was classified as right-sided if originating at the cecum, ascending colon, or transverse colon; left-sided if originating at the splenic flexure, descending colon, or sigmoid; or as rectal if originating from the rectum. Patients with rectal cancer and complete response after neoadjuvant chemoradiation and resection were staged as pT0. Extrahepatic disease was defined as any metastatic CRC (local CRC recurrence included) outside the liver detected and treated prior to or at the time of liver resection. The disease-free interval (DFI) was calculated from the time of CRC resection to the date of detection of CRLM. Positive resection margin was defined as evidence of tumor tissue at the inked resection margin (0 mm margin). Perioperative systemic chemotherapy was defined as any chemotherapy administered within 6 months prior to or after surgery. A distinction was made between oxaliplatin- and irinotecan-based regimes, 5-FU only, and no systemic chemotherapy. Genomic alterations (i.e., KRAS and BRAF) were determined increasingly in recent years. Histopathological Growth Patterns (HGPs) were assessed on hematoxylin and eosin slides of resection specimens.[23] The HGP describes the interface morphology between tumor cells and normal liver parenchyma. Two clinically relevant phenotypes are recognized; a desmoplastic and a non-desmoplastic type. CRLM displaying any replacement or pushing HGP were considered non-desmoplastic.[9]

Statistical analysis

The primary endpoint in the analyses was OS, which was calculated from the time of resection to the time of death or last follow-up. Continuous factors were compared using the Mann-Whitney U test and categorical factors using the Chi-square test. Missing data were multiply imputed by chained equations to avoid loss of information due to case-wise deletion.[24] Multivariable Cox proportional hazards regression analyses were performed including predictors that are known to be associated with OS, including age, gender, location CRC, nodal status CRC, disease-free interval between date resection CRC and diagnosis of CRLM, number of CRLM, diameter of largest CRLM, preoperative CEA, resection margin, extrahepatic disease, KRAS mutation status, BRAF mutation status, histopathological growth pattern, and perioperative systemic chemotherapy, and perioperative HAIP

chemotherapy.[25] Three-knot restricted cubic splines were used to assess linearity of continuous factors.[26]

The model discrimination was evaluated by the time-dependent area under the receiver operating characteristic (ROC) curve (AUC). The AUC was based on weighting by the inverse probability of censoring at 10-years.[27] Discrimination was evaluated with a leave-one-study-out cross-validation. That is, in each validation step, one center is used to develop the model while the other is used as a validation set to provide the performance of the models in the two centers, although both centers were used to estimate the absolute risk.[28] External validity was assessed according to the AUCs of both centers. The 95% prediction intervals (PI) indicated the likely range for the discrimination performance of the model in a new dataset. Calibration was assessed visually by plotting the predicted probability against the actual observed frequency of predicted outcomes at 10 years.[29] The discriminative power of the model was compared with the clinical risk score (CRS) by Fong and the GAME score by Margonis using the likelihood ratio test.[8, 30]

A separate multivariable model with dichotomized factors was used to develop a simplified risk score. Backward selection with stepwise elimination of factors with a p-value >0.20 was performed. Points for the score were determined by multiplying each regression coefficient by 5 rounded to integers.[31] Next, four risk groups were proposed based on observed 10-year OS probabilities.

A p-value of <0.05 was considered as statistically significant. Analyses were performed in RStudio (Rstudio, version 1.0.153, Boston, MA). The protocol of this study was approved by the Institutional Review Board of MSKCC (IRB number 16-533) and Erasmus MC (MEC-2020-0294).

Results

A total of 4539 patients underwent curative-intent surgery for CRLM at the two centers during the study period. Reasons for exclusion were: incomplete liver resection (n = 251, 6%), residual extrahepatic disease (n = 124, 3%), and no colorectal resection (n = 52, 1%). The final group included 4112 patients; 3064 patients (75%) from MSKCC (period 1992-2019) and 1048 patients (25%) from Erasmus MC (period 2000-2019).

Patient characteristics

The median age was 61 years (Interquartile range (IQR) 52-69 years, Table 1). The majority of patients (n = 3366, 82%) had a resection since 2000. Extrahepatic disease was resected or ablated before or at the time of resection of CRLM in 468 patients (11%). KRAS mutational status was available in 1567 patients (38%) and mutated in 639 (41%). BRAF mutational status was available in 1358 patients (33%) and mutated in 55 patients (4%). HGP could be

assessed in 3136 patients (76%), and a desmoplastic HGP was found in 470 patients (22%). Perioperative systemic chemotherapy was administered in 3042 patients (74%); additional HAIP chemotherapy was administered in 1061 patients (26%). During follow-up 2372 patients died. The median follow-up for survivors was 99 months (IQR 53-160 months). Median follow-up was 98 months (IQR 48-167) at MSKCC and 102 months (IQR 65-144) at Erasmus MC.

Disease status at 10-years of follow-up

Of 2389 patients who had the initial CRLM resection at least 10-years ago, 510 (21%) patients were alive at 10-years of follow-up. Of those patients, 171 patients developed a recurrence during the initial 10-year follow-up; 133 (78%) underwent complete resection of all recurrent disease and were alive without evidence of disease at 10 years. The remaining 38 patients (22%) were alive with disease at 10-years follow-up. The median follow-up of survivors beyond at 10-years was 170 months (95% CI 166-174). Nine patients (2% of all patients alive at 10 years) developed a recurrence after 10-years follow-up.

Table 1. Patient characteristics and 10-year OS probabilities

		Erasmus MC (%)	MSKCC (%)	Total (%)	Median OS			10-year OS	
					Months	95% CI	P-value	%	95% CI
Total number of patients		1048 (25)	3064 (75)	4112					
PATIENT CHARACTERISTICS									
Age	*Median (IQR)*	64 (58-71)	60 (50-68)	61 (52-69)			<0.001		
	=<60 years	349 (33)	1594 (52)	1943 (47)	65	60-69		35	33-38
	>60 years	699 (67)	1470 (48)	2169 (53)	56	53-59		26	24-29
Gender							0.19		
	Female	367 (35)	1323 (43)	1690 (41)	58	54-63		33	29-35
	Male	681 (65)	1741 (57)	2422 (59)	60	57-65		29	27-31
Year of surgery							<0.001		
	<2000	0	746 (24)	746 (18)	47	42-51		25	22-29
	≥2000	1048 (100)	2318 (76)	3366 (82)	63	60-67		32	30-34
DISEASE CHARACTERISTICS									
Location CRC							<0.001		
	Right-sided	192 (19)	836 (28)	1028 (26)	49	47-54		27	24-31
	Left-sided	454 (44)	1402 (47)	1856 (47)	65	61-70		33	30-35
	Rectum	379 (37)	725 (25)	1104 (28)	58	55-64		29	26-33
	Missing	23	101	124					
pT-stage							0.002		
	*0**	26 (3)	13 (1)	39 (1)	94	63-NR		37	19-69
	1	14 (1)	85 (3)	99 (3)	105	59-155		47	36-61
	2	146 (14)	287 (10)	433 (11)	66	58-74		35	31-41
	3	731 (71)	1984 (72)	2715 (72)	58	56-63		30	28-32
	4	113 (11)	398 (14)	511 (13)	50	42-58		26	21-32
	Missing	18	297	315					

(Continued)		Erasmus MC (%)	MSKCC (%)	Total (%)	Median OS			10-year OS	
					Months	95% CI	P-value	%	95% CI
pT-stage							0.003		
	T 0-2	186 (18)	385 (14)	571 (15)	67	63-82		37	33-42
	T 3-4	844 (82)	2382 (86)	3226 (85)	57	55-61		30	28-32
	Missing	18	297	315					
Nodal status CRC							<0.001		
	N0	421 (41)	1126 (37)	1547 (39)	75	71-82		39	36-42
	N1	392 (38)	1168 (39)	1560 (38)	55	52-59		26	24-29
	N2	211 (21)	736 (24)	947 (23)	47	43-50		23	20-26
	Missing	22	43	65					
Nodal status CRC							<0.001		
	N0	420 (41)	1127 (37)	1547 (38)	75	71-82		39	36-42
	N+	609 (59)	1906 (63)	2515 (62)	52	50-55		25	23-27
	Missing	19	31	50					
Disease-free interval							0.24		
	≤ 12 months	734 (70)	2085 (68)	2819 (69)	57	55-60		30	28-32
	> 12 months	314 (30)	973 (32)	1287 (31)	64	59-70		31	28-34
	Missing	0	6	6					
Number CRLM							<0.001		
	1	452 (44)	1252 (41)	1704 (42)	71	66-76		35	32-38
	2	211 (20)	598 (20)	809 (20)	60	55-68		32	29-36
	3	118 (11)	391 (13)	509 (13)	55	49-58		29	24-34
	4	89 (9)	233 (8)	322 (8)	51	46-58		28	22-34
	5-9	139 (13)	451 (15)	590 (15)	47	42-52		23	19-28
	≥10	29 (3)	115 (4)	144 (4)	38	34-48		14	8-26
	Missing	10	24	34					

(Continued)		Erasmus MC (%)	MSKCC (%)	Total (%)	Median OS Months	95% CI	P-value	10-year OS %	95% CI
Extrahepatic disease**							<0.001		
	No	940 (90)	2704 (88)	3644 (89)	63	60-67		32	31-34
	Yes	108 (10)	360 (12)	468 (11)	40	37-45		14	11-19
Size largest tumor							<0.001		
	≤ 5cm	823 (83)	2285 (76)	3108 (78)	65	62-68		33	31-36
	> 5cm	163 (17)	729 (24)	892 (22)	43	39-48		22	19-26
	Missing	62	50	112					
Preoperative CEA							<0.001		
	≤ 200 µg/L	899 (92)	2497 (91)	3396 (92)	61	58-65		32	30-34
	> 200 µg/L	80 (8)	234 (9)	314 (8)	48	41-51		19	14-25
	Missing	69	333	402					
Resection margin involved							<0.001		
	No	844 (85)	2686 (89)	3530 (88)	63	59-66		32	30-34
	Yes	155 (15)	335 (11)	490 (12)	42	37-46		17	13-21
	Missing	49	43	92					
KRAS mutational status							<0.001		
	Wildtype	131 (61)	797 (59)	928 (59)	78	72-86		34	30-39
	Mutated	85 (39)	554 (41)	639 (41)	53	49-58		27	22-32
	Missing	832	1713	2545					
BRAF mutational status							<0.001		
	Wildtype	183 (97)	1120 (96)	1303 (96)	72	66-79		33	29-37
	Mutated	6 (3)	49 (4)	55 (4)	40	35-70		22	11-46
	Missing	859	1895	2754					
Histopathological growth pattern							<0.001		
	dHGP	216 (24)	254 (21)	470 (22)	86	75-104		41	36-48
	non-dHGP	696 (76)	970 (79)	1666 (78)	57	51-59		26	23-29
	Missing	136	1840	1976					

TREATMENT CHARACTERISTICS									
Perioperative systemic CTx							<0.001		
	No CTx	546 (53)	241 (9)	787 (21)	53	48-60		26	22-30
	5-FU only	25 (2)	549 (20)	574 (15)	53	50-59		28	24-32
	OXA- or	461 (45)	2007 (71)	2468 (64)	64	60-68		34	32-36
	IRINO	16	267	283					
Perioperative HAIP CTx							<0.001		
	No	1037 (99)	2014 (66)	3051 (74)	55	53-58		27	25-29
	Yes	11 (1)	1050 (34)	1061 (26)	73	68-83		40	36-43

Abbreviations: CEA: carcinoembryonic antigen, CI: confidence interval, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, HAIP: hepatic arterial infusion pump chemotherapy, HGP: histopathological growth pattern. IRINO: irinotecan, IQR: interquartile range, OXA: oxaliplatin, NR: not reached, pT-stage: pathology tumor stage

*Rectal cancer with complete response after neoadjuvant chemoradiotherapy.
** Resected prior or during CRLM resection

10-year OS for patient, tumor, and treatment characteristics

Estimated median OS for the whole cohort was 59 months (95% CI 57-62 months) with an estimated 5-year OS of 49% (95% CI 48-51) and a 10-year OS of 30% (95% CI 29-32%). Poor prognostic factors associated with a 10-year OS probability below 20% were extrahepatic disease before or at time of CRLM resection (14%, 95% CI 11-19%), 10 or more CRLM (14%, 95% CI 8-26%), a CEA level of more than 200 µg/L (19%, 95% CI 14-25%), and a positive resection margin (17%, 95% CI 13-21%, Table 1). Favorable prognostic factors associated with a 10-year OS rate above 40% were pT1 CRC (47%, 95% CI 36-61%), and desmoplastic HGP (41%, 95% CI 36-48%). Genomic alterations were associated with intermediate 10-year OS: 34% (95% CI 30-39%) for KRAS mutants and 33% (95% CI 29-37%) for BRAF mutants (Table 1).

Perioperative oxaliplatin- or irinotecan-based systemic chemotherapy was associated with a 10-year OS probability of 34% (95% CI 32-36%), compared to 28% (95% CI 24-32%) for 5-FU only systemic chemotherapy, and 26% (95% CI 22-30%) for no perioperative systemic chemotherapy ($p < 0.001$). Perioperative HAIP chemotherapy was associated with a 10-year OS probability of 40% (95% CI 36-43%) compared to 27% (95% CI 25-29%) without perioperative HAIP chemotherapy ($p < 0.001$).

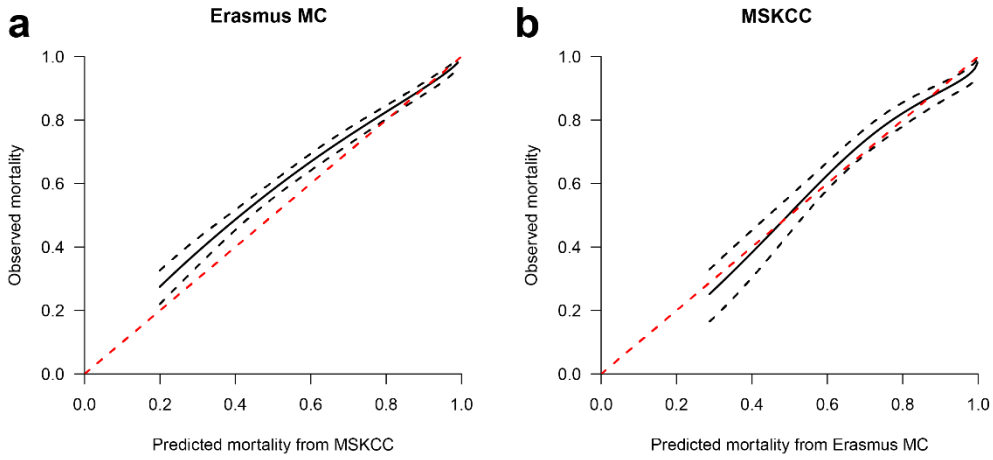
Individual probability of 10-year OS

Fifteen prognostic factors for 10-year OS were included: age, gender, location CRC, nodal status CRC, disease-free interval, number of CRLM, diameter of largest CRLM, preoperative CEA, resection margin, extrahepatic disease, KRAS mutation status, BRAF mutation status, histopathological growth pattern, perioperative systemic chemotherapy, and perioperative HAIP chemotherapy (Table 2). The 10-year OS probability for individual patients can be estimated using the web-based calculator (https://dhoppener.shinyapps.io/10yos/) or the equation in the supplements. The AUC of this model was 0.73 with internal-external cross-validation for both centers (Erasmus MC 0.73, 95% CI 0.68-0.78; MSKCC 0.73, 95% CI 0.70-0.75).

Calibration showed slight underestimation of the model developed in Erasmus MC and validated in MSKCC. Calibration was acceptable the model developed in MSKCC and validated in Erasmus MC (Figure 1). Interactions between center and all candidate predictors were not statistically significant ($p > 0.05$).

Figure 1. Calibration plots in the Erasmus and MSKCC cohort

A) Full model developed in Erasmus MC and validated in MSKCC
B) Full model developed in MSKCC and validated in Erasmus MC



The black solid lines represent the predicted and observed mortality. The black dotted lines are the 95% prediction intervals. Perfect calibration would be present if the solid black line would overlap the red dotted line.

The current model outperformed the CRS by Fong (AUC 0.62, 95% CI 0.59-0.64, $p < 0.001$) and the GAME score by Margonis (AUC 0.66, 95% CI 0.64-0.69, $p < 0.001$) that have been developed for patients with resectable CRLM, but did not focus on long-term OS.

Table 2. Multivariable Cox regression analysis

Covariate	HR	95% CI	P-value
Age (10 year increase)	1.31	1.23-1.40	<0.001
Gender (male)	1.15	1.06-1.25	0.001
Location CRC			
Right-sided		REF	
Left-sided	0.90	0.81-0.99	0.04
Rectum	1.04	0.93-1.17	0.45
Node-positive CRC	1.45	1.33-1.59	<0.001
Disease-free interval	0.996	0.993-0.999	0.01
pT-stage (pT3-4)	1.03	0.91-1.15	0.65
Number CRLM	1.11	1.10-1.14	<0.001
Diameter CRLM (cm)	1.09	1.07-1.11	<0.001
Preoperative CEA level	1.003	1.001-1.005	0.004
Positive resection margin	1.40	1.24-1.58	<0.001
Extrahepatic disease	1.62	1.44-1.83	<0.001
Perioperative systemic CTx			
No CTx		REF	
5-FU only	0.83	0.73-0.95	0.005
OXA- or IRINO-based	0.84	0.74-0.94	0.003
Perioperative HAIP CTx	0.73	0.65-0.81	<0.001
KRAS mutant	1.59	1.46-1.73	<0.001
BRAF mutant	1.69	1.42-2.01	<0.001
Non-dHGP	1.57	1.40-1.77	<0.001

Abbreviations: CEA: carcinoembryonic antigen, CI: confidence interval, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, HAIP: hepatic arterial infusion pump chemotherapy, HGP: histopathological growth pattern. IRINO: irinotecan, IQR: interquartile range, OXA: oxaliplatin, NR: not reached, pT-stage: pathology tumor stage

Simplified risk score

A simplified risk score with 13 dichotomized prognostic factors is presented in Table 3. The prognostic factors are the same as in the model with continuous factors, except for disease-free interval and location CRC dropping out of the model. The risk score is calculated by adding points for poor prognostic factors and subtracting points for treatment effects. The cumulative score ranges from -3 to 17. Four groups were identified; favorable (≤ 3 points), intermediate (4-5 points), unfavorable (6-8 points), and very unfavorable (≥ 9 points) with corresponding 10-year OS (95% CI) probabilities of 57% (51-60%; n = 692), 38% (34-42%, n = 993), 24% (23-29%, n = 1483), and 12% (10-15%, n = 944) respectively (Figure 2).

Table 3. Simplified risk score for 10-year OS

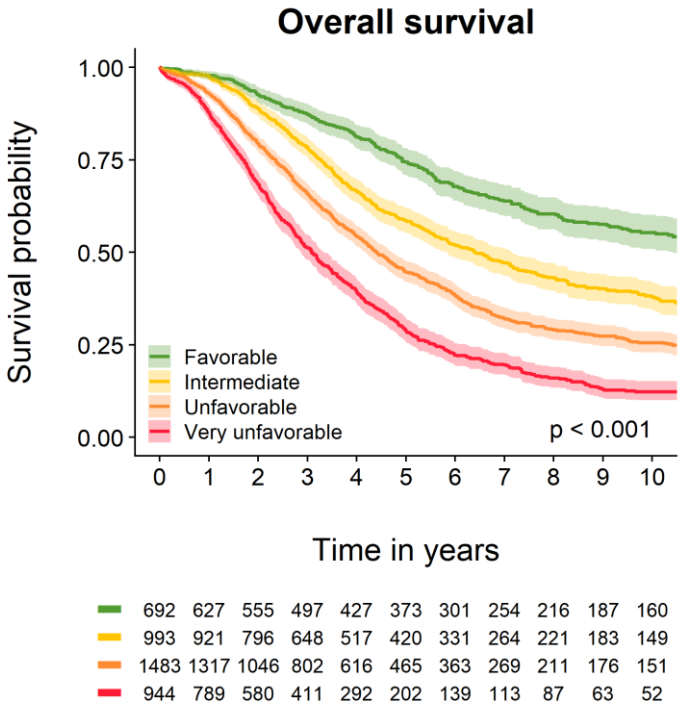
Prognostic factors	**HR**	**95% CI**	**Points**
Age > 60 years	1.31	1.20-1.42	**2**
Gender (male)	1.15	1.06-1.25	**1**
Node positive CRC	1.47	1.35-1.60	**2**
More than one CRLM	1.37	1.26-1.50	**2**
Size CRLM > 5 cm	1.44	1.31-1.58	**2**
Preoperative CEA > 200 µg/L	1.13	0.99-1.30	**1**
Positive resection margin	1.48	1.32-1.66	**2**
Extrahepatic disease	1.57	1.39-1.77	**3**
KRAS mutant	1.58	1.45-1.72	**3**
BRAF mutant	1.74	1.46-2.07	**3**
Non-dHGP	1.63	1.45-1.83	**3**
Perioperative systemic CTx*	0.86	0.78-0.96	**-1**
Perioperative HAIP CTx	0.75	0.68-0.84	**-2**

Groups	Sample size	10-year OS (%)	95% CI	Points
Favorable	711	57	53-62	≤ 3
Intermediate	952	38	34-42	4 – 5
Unfavorable	1585	24	21-26	6 – 8
Very unfavorable	846	12	10-15	≥ 9

Abbreviations: CI: confidence interval, CRC: colorectal cancer, CRLM: colorectal liver metastases, CTx: chemotherapy, HAIP: hepatic arterial infusion pump chemotherapy, HR: hazard ratio, non-dHGP: non-desmoplastic histopathological growth pattern

*Including 5-FU and oxaliplatin- or irinotecan-based perioperative systemic chemotherapy

Figure 2. Kaplan-Meier of overall survival



Discussion

The current model predicts with a web-based calculator the individual patient's probability of 10-year OS after resection of CRLM with reasonable accuracy. Fifteen prognostic factors were identified, including two patient factors (age and gender), eight tumor characteristics (location CRC, nodal status CRC, disease-free interval, number CRLM, diameter CRLM, preoperative CEA, resection margin, extrahepatic disease), three tumor biomarkers (KRAS mutation status, BRAF mutation status, and HGP), and two treatments (perioperative systemic and HAIP chemotherapy). The simplified risk score distinguishes four groups with a 10-year OS ranging from 12% to 57%. This is the first clinical prediction model for OS after resection of CRLM that incorporates BRAF and HGP. Moreover, treatment factors were incorporated in addition to patient and tumor characteristics.

Several studies have reported 10-year OS after resection of CRLM.[2-7] In a meta-analysis of eleven studies, together representing 2387 patients, the estimated 10-year OS ranged from 12% to 37%.[3] Two prognostic models predicted 10-year OS, but considered only a subset of known prognostic factors.[2, 4] Moreover, both models were developed using logistic regression analyses, which introduced bias by excluding patients lost to follow-up before 10-years.

Most published prognostic models focused on recurrence of disease and short-term OS and had a small sample size below 1000 patients.[8, 30, 32-37] One of the first models was the clinical risk score (CRS) by Fong et al.(30) The score is based on five prognostic factors; DFI, nodal status, number of CRLM, size of CRLM, and preoperative serum CEA level. The strength of the score is its simplicity with one point assigned to each factor. However, the score was developed to predict recurrence, included only 5 factors, and did not consider treatment and genomic alterations. These aspects may explain the poor performance of the CRS score in external validations (range C-index 0.53-0.56).[38-40]

Several studies have demonstrated that KRAS mutation is an important prognostic factor for OS after resection of CRLM.[8, 41-44] In the largest study with 2655 patients in the National Cancer Database, KRAS status was an independent prognostic factor for OS (adjusted HR 1.21 95% CI 1.04-1.39, p = 0.012).[44] Two recent models have included KRAS mutation as a prognostic factor.[8, 36] However, both the GAME model and the model of Goffredo et al. did not account for several known prognostic patient and tumor factors. The present study confirmed that KRAS is an independent poor prognostic factor for 10-year OS with an adjusted HR of 1.59 (95% CI 1.46-1.73). Moreover, the current model included BRAF mutation as prognostic factor with an adjusted HR of 1.7. Our model outperforms both the CRS and GAME score in its discriminative power.

A non-desmoplastic HGP was recently identified as a strong and independent poor prognostic factor.[9] Other studies demonstrated that a non-desmoplastic HGP is associated with positive

resection margins and unsalvageable recurrences, both representing aggressive tumor biology.[10, 45, 46] The current study identified HGPs as in independent prognostic factor for 10-year OS with an adjusted HR of 1.6 for non-HGP.

The current model also contains two post-surgery treatment factors, being systemic and HAIP chemotherapy. Two RCTs could not demonstrate superior OS of perioperative systemic chemotherapy for patients undergoing resection of CRLM.[17, 47] These studies randomized about 300 patients and included mostly patients with a favorable risk profile (e.g., low number of CRLM). In the present study, perioperative oxaliplatin- or irinotecan-based systemic chemotherapy was an independent favorable factor for 10-year OS with an adjusted HR of 0.8. 5-FU without oxaliplatin or irinotecan was also a favorable prognostic factor compared to no perioperative chemotherapy with an adjusted HR of 0.8. However, the likelihood of bias in our data is high due to the retrospective design of this study. In the present study 26% of patients received perioperative HAIP chemotherapy, which was an strong independent prognostic factor for 10-year OS (adjusted HR 0.7).[15, 18] Long-term follow-up of a randomized controlled trial found a 10-year OS of 41% with adjuvant HAIP chemotherapy and 5-FU versus 27% with 5-FU alone ($p = 0.10$).[18] Long-term follow-up of four phase II-III trials reported a 10-year OS of 61% (95% CI 51%-70%) for patients treated after 2003.[48] An ongoing phase III RCT investigates adjuvant HAIP chemotherapy in the current era.[49]

A previous paper investigating 10-year OS after resection of CRLM concluded that none of the poor prognostic risk factors precluded cure.[1, 2] In the present, much larger study, we identified additional independent poor prognostic factors for 10-year OS (i.e., KRAS and BRAF mutation and HGP). Again, none of these factors precluded 10-year OS, although several papers found a very poor prognosis in patients with BRAF mutation.[50, 51] The probability of cure after resection of CRLM was 12% in the worst group of patients who had a combination of many poor prognostic factors (i.e., at least 9 points in the simplified risk score). This justifies curative-intent surgery for selected patients regardless of a combination of poor prognostic factors.

This study has several limitations. Firstly, the study has a quite long follow-up. This strength is also its potential weakness: patient selection and treatment may have changed during 26 years. However, only 18% of patients underwent resection prior to 2000 and 15 prognostic factors including two treatment factors largely accounted for changes over time. Secondly, the two centers differed in perioperative treatment. In MSKCC, over 90% of patients received perioperative systemic chemotherapy, which has been the standard of care in many countries. In the Netherlands, patients did receive systemic induction chemotherapy for (borderline) unresectable disease, but most patients with resectable disease did not receive perioperative chemotherapy according to Dutch guidelines. Moreover, perioperative HAIP chemotherapy has been performed regularly at MSKCC, whereas at Erasmus MC only during the last year within clinical trials.(20) These differences between centers are in fact also a strength of the

model, since the dataset included patients with similar characteristics who did and did not receive perioperative systemic and/or HAIP chemotherapy. This allowed for assessment of treatment effects and improved generalizability (i.e., external validity) of the model, as reflected by an AUC of 0.73 at cross-validation and the acceptable calibration. Thirdly, the model may appear applicable only in centers that offer HAIP chemotherapy. However, the model included more than 3000 patients who did not receive perioperative HAIP chemotherapy. The model and simplified score can be applied to patients who did and did not receive perioperative HAIP chemotherapy. Fourthly and lastly, genomic alterations in KRAS and BRAF, as well as HGP status were missing for many patients. This was accounted for by multiple imputation, which is methodologically superior to excluding patients with missing data.[52]

In conclusion, this model with web-based calculator accurately predicts 10-year OS after resection of CRLM based on 15 patient, tumor, genomic, and treatment factors. This may be used to inform patients and clinicians or stratify patients in clinical trials.

References

1. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
2. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? *Surgery* 2018; 163(6):1238-1244.
3. Abbas S, Lam V, Hollands M. Ten-year survival after liver resection for colorectal metastases: systematic review and meta-analysis. *ISRN Oncol* 2011; 2011:763245.
4. Kulik U, Plohmann-Meyer M, Gwiasda J, et al. Proposal of Two Prognostic Models for the Prediction of 10-Year Survival after Liver Resection for Colorectal Metastases. *HPB Surg* 2018; 2018:5618581.
5. Cucchetti A, Ferrero A, Cescon M, et al. Cure model survival analysis after hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 2015; 22(6):1908-14.
6. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4:283-301.
7. Galjart B, van der Stok EP, Rothbarth J, et al. Posttreatment Surveillance in Patients with Prolonged Disease-Free Survival After Resection of Colorectal Liver Metastasis. *Ann Surg Oncol* 2016; 23(12):3999-4007.
8. Margonis GA, Sasaki K, Gholami S, et al. Genetic And Morphological Evaluation (GAME) score for patients with colorectal liver metastases. *Br J Surg* 2018.
9. Galjart B, Nierop PMH, van der Stok EP, et al. Angiogenic desmoplastic histopathological growth pattern as a prognostic marker of good outcome in patients with colorectal liver metastases. *Angiogenesis* 2019; 22(2):355-368.
10. Höppener DJ, Galjart B, Nierop PMH, et al. Histopathological Growth Patterns and Survival After Resection of Colorectal Liver Metastasis: An External Validation Study. *JNCI Cancer Spectr* 2021; 5(3):pkab026.
11. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371(9617):1007-16.
12. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; 15(6):601-11.
13. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.
14. Ayez N, van der Stok EP, de Wilt H, et al. Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver

metastases: the CHARISMA randomized multicenter clinical trial. *BMC Cancer* 2015; 15:180.
15. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017:JCO2016718346.
16. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.
17. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-1215.
18. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
19. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015; 162(1):W1-73.
20. https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html.
21. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. *Mol Cancer Ther* 2009; 8(5):1015-25.
22. Buisman FE, Grunhagen DJ, Homs MYV, et al. Adjuvant Hepatic Arterial Infusion Pump Chemotherapy After Resection of Colorectal Liver Metastases: Results of a Safety and Feasibility Study in The Netherlands. *Ann Surg Oncol* 2019.
23. van Dam PJ, van der Stok EP, Teuwen LA, et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 2017.
24. Resche-Rigon M, White IR, Bartlett JW, et al. Multiple imputation for handling systematically missing confounders in meta-analysis of individual participant data. *Stat Med* 2013; 32(28):4890-905.
25. D.R. C. Regression Models and Life-Tables. *Journal of the Royal Statiscial Society* 1972; 34(2):187-220.
26. Harrel FE. Regression Modeling Strategies: with applications to linear models, logistic and ordinal regression, and survival analysis: Springer, 2015.
27. E.W. S. Clinical prediciton models: a practical approach to developmentm validation and updating. New York: Springer, 2010.
28. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016; 69:245-7.
29. Austin PC, Harrell FE, Jr., van Klaveren D. Graphical calibration curves and the integrated calibration index (ICI) for survival models. *Stat Med* 2020; 39(21):2714-2742.

30. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230(3):309-18; discussion 318-21.
31. Sullivan LM, Massaro JM, D'Agostino RB, Sr. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004; 23(10):1631-60.
32. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver Int* 2009; 29(1):89-102.
33. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008; 247(1):125-35.
34. Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2012; 19(1):72-84.
35. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg* 1999; 189(3):291-9.
36. Liu W, Wang K, Han Y, et al. Nomogram predicted disease free survival for colorectal liver metastasis patients with preoperative chemotherapy followed by hepatic resection. *Eur J Surg Oncol* 2019.
37. Kanemitsu Y, Kato T. Prognostic models for predicting death after hepatectomy in individuals with hepatic metastases from colorectal cancer. *World J Surg* 2008; 32(6):1097-107.
38. Roberts KJ, White A, Cockbain A, et al. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. *Br J Surg* 2014; 101(7):856-66.
39. Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg* 2007; 246(2):183-91.
40. Reddy SK, Kattan MW, Yu C, et al. Evaluation of peri-operative chemotherapy using a prognostic nomogram for survival after resection of colorectal liver metastases. *HPB (Oxford)* 2009; 11(7):592-9.
41. Margonis GA, Amini N, Buettner S, et al. The Prognostic Impact of Primary Tumor Site Differs According to the KRAS Mutational Status: A Study By the International Genetic Consortium for Colorectal Liver Metastasis. *Ann Surg* 2019.
42. Brudvik KW, Kopetz SE, Li L, et al. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. *Br J Surg* 2015; 102(10):1175-83.
43. Gholami S, Kemeny NE, Boucher TM, et al. Adjuvant Hepatic Artery Infusion Chemotherapy is Associated With Improved Survival Regardless of KRAS

Mutation Status in Patients With Resected Colorectal Liver Metastases: A Retrospective Analysis of 674 Patients. *Ann Surg* 2019.

44. Goffredo P, Utria AF, Beck AC, et al. The Prognostic Impact of KRAS Mutation in Patients Having Curative Resection of Synchronous Colorectal Liver Metastases. *J Gastrointest Surg* 2018.
45. Nierop PMH, Galjart B, Hoppener DJ, et al. Salvage treatment for recurrences after first resection of colorectal liver metastases: the impact of histopathological growth patterns. *Clin Exp Metastasis* 2019; 36(2):109-118.
46. Nierop PMH, Hoppener DJ, van der Stok EP, et al. Histopathological growth patterns and positive margins after resection of colorectal liver metastases. *HPB (Oxford)* 2019.
47. Ychou M, Hohenberger W, Thezenas S, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. *Ann Oncol* 2009; 20(12):1964-70.
48. Kemeny NE, Chou JF, Boucher TM, et al. 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* 2016.
49. Buisman FE, Homs MYV, Grunhagen DJ, et al. 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* 2019; 19(1):327.
50. Margonis GA, Buettner S, Andreatos N, et al. Association of BRAF Mutations With Survival and Recurrence in Surgically Treated Patients With Metastatic Colorectal Liver Cancer. *JAMA Surg* 2018; 153(7):e180996.
51. Gagnière J, Dupré A, Gholami SS, et al. Is Hepatectomy Justified for BRAF Mutant Colorectal Liver Metastases?: A Multi-institutional Analysis of 1497 Patients. *Ann Surg* 2020; 271(1):147-154.
52. Steyerberg EW. Clinical prediction models: A practical approach to development, validation, and updating (statistics for biology and health) Springer. *New York* 2009.

Supplement 1. Cox formula

The Cox regression model resulted in the following formula:

*S (t) = 0.2964218 ^ exp(0.2728 * age at resection CRLM (60, if age <60) + (0.1416, in case of male) + (-0.1069 * in case of left-sided colon cancer) + (0.0439, in case of rectal primary) + (0.3741, in case of node positive CRC) + (-0.0038 * DFI in months) + (0.0273, in case of pT3-4 CRC) + (0.1130* number of CRLM) + (0.0881* size of largest CRLM in centimeter) + (0.0029 * CEA in µg/L) + (0.3365, in case of positive resection margins) + (0.4843, in case of extrahepatic disease) + (-0.1856, in case of 5-FU systemic chemotherapy only) + (-0.1856, in case of oxaliplatin- or irinotecan-based perioperative SYS) + (-0.3204, in case of perioperative HAIP chemotherapy) + (0.4641, in case of KRAS mutant) + (0.5221, in case of BRAF mutant) + (0.4537, in case of non-dHGP)*

Abbreviations: CEA: carcinoembryonic antigen, CRC: colorectal cancer, CRLM: colorectal liver metastases, DFI: disease-free interval, HAIP: hepatic arterial infusion pump, non-dHGP: non-desmoplastic histopathological growth pattern, SYS: systemic chemotherapy

Part IV

General discussion,
future perspectives,
and summary

General discussion

This thesis investigated the value of intra-arterial and systemic chemotherapy, and prognostication and personalized treatment in patients with resectable colorectal liver metastases (CRLM). Based on the literature and results of the studies in this thesis, several questions can be addressed.

Is intra-arterial chemotherapy still relevant in the modern era of CRLM treatment?
Hepatic arterial infusion pump (HAIP) chemotherapy was developed in the late 1970s. The first randomized controlled trial (RCT) of adjuvant HAIP chemotherapy demonstrated superior 2-year overall survival in the 90s.[1] At that time, promising systemic chemotherapies such as oxaliplatin and irinotecan were introduced. Unfortunately, these new agents have demonstrated little or no survival benefit in the perioperative setting for CRLM).[1-5] Therefore, perioperative systemic chemotherapy is not recommended in patients with resectable CRLM in the Netherlands. Moreover, targeted treatments have not been able to improve survival in patients with resectable CRLM. However, up to 70% of patients develop recurrent disease within the first two years after resection and/or ablation.[6, 7] Recurrent disease is often (about 50%) confined to the liver.[6] HAIP chemotherapy has regained interest in the absence of any other effective treatment to improve survival after resection of CRLM. HAIP chemotherapy has a strong rationale, by exposing tumor cells to high drug concentrations, without systemic side effects.

Does HAIP chemotherapy improve survival?
The Memorial Sloan Cancer Institute (MSKCC), and in particular thanks to the dedication dr. Nancy Kemeny of the Department of Medical Oncology, has pioneered in the field of HAIP chemotherapy for decades. An RCT from MSKCC published in 1999 of 156 patients with resectable CRLM found a superior 2-year overall survival (OS) (86% vs. 72%, $p = 0.03$), and hepatic progression free survival (90% vs. 60%, $p < 0.001$) in patients treated with adjuvant HAIP chemotherapy.[1] Long-term follow-up of this trial also found a median superior overall progression free survival (31 months vs. 17 months, $p = 0.02$).[4] Furthermore, convincing OS benefit was found in a study including 2368 patients with resected CRLM from MSKCC.[8] In this retrospective study perioperative HAIP chemotherapy was associated with a median overall survival benefit of 23 months (89 vs. 65 months, $p < 0.001$). In propensity score analyses HAIP chemotherapy remained an independent prognostic factor (adjusted HR 0.67, 95% CI 0.59-0.76). Subgroups that benefit most were patients with node-negative colorectal cancer (129 months vs. 51 months, $p < 0.001$), and patients with a low clinical risk score (CRS)(89 months vs. 51 months, $p < 0.001$). In chapter 10 of this thesis we found that HAIP chemotherapy was associated with an estimated 10-year OS of 40% vs. 27% without HAIP chemotherapy ($p < 0.001$).[9] MSKCC has published numerous other trials demonstrating the effectiveness of HAIP chemotherapy in patients with CRLM and intrahepatic cholangiocarcinoma.[10-17]

Surprisingly, only a few specialized centers worldwide implemented HAIP programs (e.g., Memorial Sloan Kettering Cancer Center, NY, USA; University Hospital Zurich, Zurich, Switzerland; University of Pittsburgh Medical Center, Pittsburgh, PA, USA; Washington University School of Medicine, St. Louis, MO, USA; and Sunnybrook, Toronto, ON, Canada). In the past few years, there has been a revival of interest in HAIP chemotherapy inside and outside the US. This has been strengthened by observations that only little benefit was gained by new systemic chemotherapy regimens in the perioperative setting.

Which factors deterred implementation of HAIP chemotherapy?

HAIP chemotherapy was introduced and promoted by MSKCC since the 80s. However, its application outside MSKCC has been limited, regardless of superior survival after adjuvant HAIP chemotherapy demonstrated in an RCT in the New England Journal of Medicine.[1, 4] There have been numerous reasons that could have accounted for limited implementation of HAIP chemotherapy. The RCT was published in 1999 at a time when oxaliplatin and irinotecan were introduced. These systemic chemotherapies were effective in the setting of unresectable metastatic colorectal cancer. Only many years later they were shown to not improve OS in the perioperative setting.[2, 3] Moreover, many other systemic drugs were anticipated, but did not materialize.

In comparison, HAIP chemotherapy appeared a cumbersome and old-fashioned treatment with an old drug (i.e., floxuridine) approved by the FDA in 1971. In the early years of HAIP chemotherapy the reports on complications of HAIP chemotherapy such as arterial thrombosis, liver toxicity, biliary sclerosis, and pump related technical complication may have deterred centers from using it.[18-21] While these complications should be taken seriously, the incidence of pump related complications is low in experienced centers.[22] HAIP chemotherapy is a complex multidisciplinary treatment that requires considerable knowledge and skills. However, with adequate training and multidisciplinary collaboration, HAIP chemotherapy has been demonstrated to be safe and feasible.[23, 24] Over the years, several studies contributed to have improved safety of HAIP chemotherapy. Introduction of dexamethasone reduced the risk of biliary sclerosis.[10] Also, a phase II study demonstrated that bevacizumab in addition to oxaliplatin-based systemic chemotherapy regimens increased risk of biliary sclerosis with concurrent HAIP chemotherapy, without improvement of survival.[11] A German phase III RCT on intra-arterial chemotherapy (5-FU) using an external infusion pump was terminated at the interim-analysis after randomizing 226 patients due to a high rate of technical complications.[25] This may be a result of poor training and design as this study was performed in 26 centers, all with limited experience and exposure. We recently demonstrated in the Netherlands that excellent training of the entire multidisciplinary team reassures safety and feasibility of HAIP chemotherapy in high-volume centers.[23]

Implementation of HAIP chemotherapy in the European Union (EU) is challenging, because floxuridine is not registered the EU. Floxuridine was first registered by the United States Food and Drug Administration in 1971, but has never been registered in the EU. The incentive for the pharmaceutical industry to register floxuridine has been low compared to

the latest patented targeted treatment; the price of one vial floxuridine is about 75 USD (i.e., 75 USD per month). Pharmaceutical industry is more inclined to support dissemination of new cancer drugs with median monthly costs of 12.000 USD and typically a much lower clinical benefit.[26] Others have used 5-FU or oxaliplatin instead of floxuridine as intra-arterial chemotherapy. The efficacy of oxaliplatin is currently evaluated in the PACHA-01 trial. In this trial, patients with 4 or more CRLM will randomized to resection and adjuvant intra-arterial oxaliplatin using a mediport and an external pump or resection only.[27] It is import to realize that these agents have a much lower hepatic extraction rate compared to floxuridine. Consequently, the administered dose is limited because of systemic side effects and consequently, the dose in the tumor cells is much lower. Ongoing collaboration with pharmaceutical partners that have a greater societal interest should ensure availability and registration of floxuridine in the EU.

HAIP chemotherapy requires a pump for drug delivery, because the half-life of floxuridine is less than 10 minutes. No infusion pump with the intended use of intra-arterial chemotherapy is currently registered in the EU. This is another hurdle for the use of HAIP chemotherapy. Moreover, the Codman pump that has been used in the US contains Freon gas that is banned in the EU for environmental reasons. Lately, production of the Codman pump has been discontinued, demonstrating the need for alternative infusion pumps.[28]

Do we need another trial on HAIP chemotherapy?

The main criticism of HAIP chemotherapy has been that most of the clinical trials originated from MSKCC, raising concerns about generalizability. External validation of these trials strengthens the evidence for HAIP chemotherapy and may convince those that are reluctant to implement HAIP chemotherapy. In a pilot study of 20 patients, we have demonstrated the safety and feasibility of HAIP chemotherapy in two high-volume centers.[23] In the ongoing PUMP trial we investigate effectiveness of HAIP chemotherapy for patients with resectable CRLM and a low CRS.[29] The PUMP trial aims to definitively answer the question whether adjuvant HAIP chemotherapy after resection of CRLM is more effective than resection alone.

Is there any place for perioperative systemic chemotherapy in the management of patients with resectable CRLM?

The efficacy of perioperative systemic chemotherapy in patients with resectable CRLM has been questionable. A large RCT (EORTC 40983) of 364 patients found a superior progression-free survival of 21 months in per-protocol analysis of patients treated with perioperative FOLFOX with resection compared to 13 months resection only ($p = 0.04$).[2, 3] The OS curves are exactly overlapping after a median follow-up of more than 8 years ($p = 0.35$). Nevertheless, in many parts of the world, perioperative systemic chemotherapy is the standard of care. Some studies found that perioperative systemic chemotherapy appears effective only in patients with an aggressive disease biology. A subgroup analysis of the EORTC 40983 trial demonstrated that patients with a moderately elevate carcinoembryonic antigen (CEA, >5ng/mL) had improved OS with perioperative FOLFOX chemotherapy (adjusted HR 0.58, 95% CI 0.37-0.90).[30] Other studies found that patients with a high CRS

might benefit from perioperative systemic chemotherapy.[31, 32] The first study (n = 363) found that neoadjuvant may improve OS (adjusted HR 0.59, 95% CI 0.40-0.88, p = 0.009). We confirmed these results in a large study of 2020 patients from two large tertiary centers, demonstrating an improved OS in high-risk patients treated with adjuvant chemotherapy (adjusted HR: 0.78, 95% CI 0.57-0.94, p = 0.02), while no benefit was found in low-risk patients (adjusted HR 0.99, m95% CI 0.82-1.19, p = 0.51).[33] Recently we also suggested that the histopathological growth factor (HGP) might be able to identify a high-risk subgroup.[34-36] A desmoplastic HGP has been related to a superior prognosis compared to patients with a non-desmoplastic type HGP in chemo-naive patients (adjusted HR 0.54, 95% CI 0.37-0.79, p < 0.001).[34] Adjuvant systemic chemotherapy seems to improve OS in non-desmoplastic HGP (adjusted HR 0.52, 95% CI 0.37-0.73, p < 0.001). However, this was only observed in patients that were not treated with preoperative chemotherapy.

In summary, two RCTs have demonstrated convincingly that perioperative systemic chemotherapy does not improve OS when considering all patients with resectable CRLM. Retrospective studies, however, suggest benefit in subgroups in patients with a high disease burden (e.g., a high CRS). These differences may be partly or even entirely attributable to selection bias and require confirmation in an RCT.

Do we need models to predict prognosis or effectiveness of treatment?

Every clinician, consciously or subconsciously, is using prognostication and prediction in daily practice. Models are useful instruments that can be used in addition to traditional diagnostics, personal experience, and expert opinions. Models that build on large dataset that include patients, disease, and treatment characteristics may be able to improve personalized prognostication and prediction as the impact of all available factors is used to assess the effect. In CRLM patients, prediction models will be in particular worthy to identify patients that do and patients that do not benefit from perioperative systemic chemotherapy and HAIP chemotherapy. Moreover, these models are a benchmark to evaluate the value of new biomarkers. Web-based calculators (e.g., predict.nhs.uk for breast cancer) and simplified risk scores derived from these models will improve personalized medicine.

In this thesis we developed a model with 15 independent factors that were associated with 10-year survival after resection of CRLM. Four risk groups were identified based on these independent factors with a chance of 10-year OS of about 10%, 25%, 40%, and 60%. Perioperative HAIP chemotherapy was the only independent treatment factor for 10-year OS.

Future perspectives

In the next years, several crucial steps should be taken to determine and formalize the role of HAIP chemotherapy in the treatment of CRLM. The most important steps include completion of clinical trials, registration of floxuridine in the EU, registration of intra-arterial chemotherapy as intended use for available pumps, integration of HAIP chemotherapy in guidelines, and development of decision aids using individual predicted survival benefit of HAIP chemotherapy. Tailor-made perioperative therapy will optimize survival benefit, minimize toxicity, and carefully use available health care budgets.

Trials on HAIP chemotherapy

Previously, HAIP chemotherapy has been criticized for its complexity, high-costs, and complications. In addition, it has been said that results demonstrated by MSKCC do not represent the general population. Recent renewed interest offers a unique opportunity for trials to elucidate these criticisms and determine the role of HAIP chemotherapy in patients with CRLM. The first trial is the phase III multicenter RCT study on adjuvant HAIP chemotherapy in resectable CRLM.[29] This study may be able to answer to the criticism to HAIP chemotherapy. First, it will answer the question whether HAIP chemotherapy prolongs survival in resectable CRLM outside the MSKCC population. This trial will also investigate if HAIP chemotherapy is cost-effective and whether HAIP chemotherapy improves quality of life.

We have also developed a trial to evaluate the effectiveness of adjuvant HAIP chemotherapy in patients with isolated recurrent CRLM. This trial is essential since hepatic recurrences after resection and ablation are very common. Very limited evidence is currently available on any perioperative treatment for recurrent CRLM. This single arm trial, including 40 patients will investigate if adjuvant HAIP chemotherapy can improve survival in patients will resectable recurrent CRLM.

A unique opportunity for a future trial in the field of HAIP chemotherapy includes patients with unresectable CRLM confined to the liver. Currently, a multicenter phase III RCT (the CAIRO V study) in the Netherlands in patients with unresectable liver-only metastases aims to define the optimal neoadjuvant induction regimen for this patient population.[37] Previous MSKCC trials demonstrated high conversion rates and promising long-term survival in first- and second-line treatment with HAIP chemotherapy in patients with unresectable CRLM.[14, 15, 38-41] An RCT should randomize patients between the best arm of the CAIRO V study with and without additional HAIP chemotherapy. However, a first step will be a single arm multicenter safety and feasibility study in the Netherlands of HAIP chemotherapy and concurrent systemic chemotherapy in patients with unresectable CRLM confined to the liver.

Future research may also contribute to optimization of toxicity related adverse events of perioperative chemotherapy. HAIP chemotherapy in the Dutch setting is limited to patients

with normal activity of the metabolic enzyme dihydropyrimidine dehydrogenase (DPYD) as a previous study of 1103 patients reported an increased severe toxicity of fluoropyrimidine-based systemic anticancer therapy (i.e., capecitabine and fluorouracil) in patients with at DPYD variant carries.[42] A new study should investigate if there is any association of DPYD genotype and HAIP-related (floxuridine) severe toxicity. Dose individualization studies may reduce toxicity in places where HAIP chemotherapy with floxuridine is implemented and could increase the applicability of the treatment in countries where limitations by DPYD variants exist.

Future implementation of HAIP chemotherapy

If ongoing studies confirm that HAIP chemotherapy is cost-effective, than that evidence will be used to support the incorporation of HAIP chemotherapy in (inter)national guidelines. Implementation in the EU requires registration of the infusion pump for intra-arterial chemotherapy, registration of floxuridine in the EU, and dissemination of knowledge and skills arising from the trial. We will continue organizing workshops and proctoring programs for HAIP chemotherapy. This will ensure rapid implementation.

Future of perioperative systemic chemotherapy

The is an unmet need for a trial to define the role of systemic chemotherapy in patients with resectable CRLM. A previous RCT could not demonstrate an OS difference of perioperative FOLFOX, however this trial was not powered for OS.[2, 3] Previous studies suggested that systemic chemotherapy may be in particular beneficial in patients with a high burden of disease (e.g., high clinical risk score or high preoperative CEA) or an aggressive tumor biology (e.g., non-desmoplastic histopathological growth pattern).[30-32] A future trial in patients with signs of aggressive disease may elucidate the role of perioperative systemic chemotherapy.

Personalized prediction

Personalized prediction may greatly improve treatment of patients with CRLM. Although the highest level of evidence is considered to result from RCTs, in many ways the results are not always relevant for the individual patient. Strict in- and exclusion criteria are typically used to minimize heterogeneity in RCTs. Large multicenter international databases, including patients from RCTs, may improve individual prediction by using state of the art statistical methods. Several new biomarkers, such as genomic status, histopathological growth patterns, circulating tumor DNA, DNA methylation profiles, and radio(geno)mics should be evaluated in these models.

The 10-year survival model that has been developed can be used as a unique opportunity for further improvements in prediction for CRLM patients. First, this model should be externally validated. External validation can be challenging since some independent factors of our model, such as assessment of histopathological growth patterns and administration of HAIP chemotherapy, are not generally accepted in clinical practice yet. Combining data of several centers may help to construct a large database to externally validate our model.

The ideal model should incorporate only preoperative factors, which will allow preoperative assessment of potential survival benefit of different perioperative therapies (i.e., HAIP chemotherapy alone, HAIP chemotherapy with systemic chemotherapy, or systemic chemotherapy alone). Many factors (e.g., number of tumors and size of largest tumor) are often based on pathological assessment, but could also be determined on preoperative imaging. A preoperative model is important because implantation of a pump for adjuvant HAIP chemotherapy is performed in the same session as resection of the CRLM.

Conclusion

Taken all opportunities and challenges together, establishing future improvements in the treatment of CRLM will need persistence and collaborative efforts. New trials should address hypotheses on the (cost)effectiveness of perioperative treatments, strategies to minimize treatment related toxicities, and improve individualized medicine in patients with resectable CRLM.

The primary aim of this thesis has been to contribute to the scientific assessment of the effectiveness of HAIP chemotherapy for CRLM. The available evidence is already overwhelming, but concerns about generalizability and lack of widespread implementation justify this large endeavor. In a pilot study, we have already confirmed that HAIP chemotherapy is safe and feasible in two expert centers. If the PUMP trial confirms the available evidence of superior survival, HAIP chemotherapy should become available worldwide in all expert centers.

English summary

The objective of this thesis was to develop clinical trials on hepatic arterial infusion pump (HAIP) chemotherapy in patients with resectable colorectal liver metastases (CRLM), and to study factors that are associated with prognosis and prediction in CRLM patients. The results of this thesis will be evaluated in three parts. **Part I** focused on the outcomes of perioperative HAIP and systemic chemotherapy in patients with resectable CRLM. In **Part II** results off a phase II safety and feasibility study on HAIP chemotherapy in the Netherlands were discussed. Additionally, a trial protocol of a multicenter phase III randomized controlled trial (RCT) was presented. This trial is currently running in the Netherlands and was designed to investigate the efficacy of HAIP chemotherapy after resection compared to resection only in patients with CRLM confined to the liver and a low clinical risk score (CRS). **Part III** focused on the prognostic and predictive value of clinical and pathological factors after resection of CRLM. In addition, models that predict individual patient outcome were evaluated.

Part I: Outcomes of perioperative intra-arterial and systemic chemotherapy

The effectiveness of different approaches of intra-arterial chemotherapy were evaluated in a systematic review and meta-analysis in **chapter 3**. The meta-analysis demonstrated that intra-arterial chemotherapy is more effective in studies using a subcutaneous pump with floxuridine. In **chapter 4-5** rates and patterns of initial recurrence after resection of CRLM were studied in retrospective cohort studies using competing risk analyses. In **chapter 4** we focused on the impact of perioperative systemic chemotherapy on the patterns of recurrence and survival of patients with resectable CRLM. Perioperative systemic chemotherapy has not shown convincing results on survival, it is however regularly administered in many countries. Some previous studies suggested that patients with an aggressive disease biology might benefit from perioperative systemic chemotherapy while other do not. Results from our study including 2020 patients suggest that perioperative systemic chemotherapy had no association with intrahepatic recurrence, but was associated with fewer pulmonary recurrences and superior OS in patients with a high clinical risk score (CRS) only. In **chapter 5** we studied the patterns of recurrence in patients treated with HAIP chemotherapy with concurrent systemic chemotherapy compared to patients treated with systemic chemotherapy only in a cohort of two center including 2128 patients. The results of this study suggest that HAIP chemotherapy is associated with a lower cumulative incidence of intrahepatic recurrence compared to patients treated with systemic chemotherapy only. The value of adjuvant HAIP chemotherapy in patients after resection or ablation of recurrent disease confined to the liver was studied in **chapter 6**. The results of this explorative retrospective analysis including 374 patients suggest that HAIP chemotherapy (n = 81) after local treatment of CRLM is associated with improved hepatic disease-free survival and OS. Although promising, the hypothesis generated by this study should be confirmed in a prospective study (PUMP III, NTR NL9294).

Part II: Clinical trials on hepatic arterial infusion pump chemotherapy

Results of a phase II safety and feasibility study of patients treated with HAIP chemotherapy after resection of CRLM are evaluated in **chapter 7**. In this study, 20 patients were included in the Erasmus MC Cancer Institute (Rotterdam) and the Netherland Cancer Institute (Amsterdam). Patients were treated with a maximum of 6 cycle of HAIP chemotherapy. This study demonstrated 90-day postoperative HAIP-related complications in 2 patients (10%). Both patients required a reoperation (without laparotomy); one patient to replace a pump with a slow pump rate, and another patient to reposition a flipped pump. All patients received the first those of HAIP chemotherapy, which was uneventful in all patients. In **chapter 8** we described the study protocol of the multicenter phase III randomized controlled PUMP trial, which was developed to investigate the efficacy of adjuvant HAIP chemotherapy with resection compered to resection only in patients with a low CRS. This trial is ongoing and recruiting, and a total number of 230 patients will be randomized. Patients with resectable CRLM, without extrahepatic disease and a CRS are eligible for inclusion. This population was selected based on a large retrospective study of 2368 patients of the Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA). A median OS was 67 months found in patients treated with HAIP chemotherapy (n = 785) compared to 44 months in patients treated with resection only (n = 1583, $p < 0.001$). The benefit of HAIP was even higher for patients with a low CRS (89 months vs. 53 months, $p < 0.001$) compared to patients with a high CRS (50 months vs. 37 months, $p < 0.001$).

Part III: Prognostication, prediction, and personalized treatment

In **chapter 9** we investigated a biomarker that could predict the effectiveness of adjuvant systemic chemotherapy after resection of CRLM. Recently, large cohort studies demonstrated that the histopathological growth pattern (HGP) of CRLM is an independent prognostic factor for survival after resection of CRLM. The HGP is represented by the interface (border) of tumor cells and normal liver parenchyma. Three type of growth patterns can be identified; the desmoplastic type growth pattern, in which tumor cells and liver parenchyma are divided by a desmoplastic rim; the replacement type HGP, in which tumor cells infiltrate the normal liver parenchyma along vascular structures; and the pushing type HGP, in which the normal liver parenchyma is pushed way and compressed by the tumor cells. The pushing type HGP is a rare HGP that has similar survival characteristics as the replacement type HGP. The replacement, pushing and mixed type HGPs can be identified as the non-desmoplastic type HGP. Our study of 1236 patients from two centers suggested that patients with a non-desmoplastic type HGP has superior OS with adjuvant systemic chemotherapy. This was observed in patients that were not pretreated with chemotherapy only. In **chapter 10** we described the results of a study including 4112 patients that was performed to develop a model for individual 10-year survival after resection of CRLM based on patient, tumor, and treatment characteristics. Ten-year estimated OS was 30%. Fifteen patient, tumor and treatment characteristics were independent prognostic factors (discrimination: 0.73). A simplified score was built to categorize patients into very unfavorable, unfavorable, intermediate, and favorable groups regarding the likelihood of 10-

year OS. These four groups related to a 10-year OS probability of approximately 10%, 25%, and 40% and 60% chance of 10-year OS.

Nederlandse samenvatting

Het proefschrift is opgedeeld in drie delen. **Deel I** focust zich op retrospectief onderzoek over de effectiviteit van intra-arteriële en systemische chemotherapie voor patiënten met resectabele colorectale levermetastasen (CRLM). In **deel II** zijn de resultaten besproken van een onderzoek naar de veiligheid en haalbaarheid van adjuvante hepatic arterial infusion pump (HAIP) chemotherapie. Tevens is het onderzoeksprotocol van een multicenter fase III gerandomiseerd onderzoek gepresenteerd. In deze studie wordt de effectiviteit van adjuvante HAIP chemotherapie na resectie van CRLM vergeleken met resectie zonder aanvullende chemotherapie in patiënten met een lage clinical risk score (CRS). De resultaten van dit onderzoek worden binnen enkele jaren verwacht. **Deel III** richt zich op de prognostische en predictieve waarde van klinische en pathologische factoren van patiënten met resectabele CRLM.

Deel I. Uitkomsten van perioperatieve intra-arteriële en systemische chemotherapie

De effectiviteit van verschillende benaderingen van intra-arteriële chemotherapie is onderzocht in een systematic review en meta-analyse in **hoofdstuk 3**. Intra-arteriële chemotherapie lijkt het meest effectief te zijn bij toediening van floxuridine via een implanteerbare pomp. In **hoofdstuk 4 en 5** zijn de recidiefpatronen na resectie van CRLM onderzocht in retrospectieve analyses waarbij het effect van verschillende behandelingen is vergeleken door middel van competing risk analyse. In **hoofdstuk 4** is peroperatieve systemische chemotherapie vergeleken met een resectie zonder aanvullende chemotherapie. Het effect van perioperatieve systemische chemotherapie op de overleving van patiënten met resectabele CRLM is onzeker, echter in veel landen buiten Nederland wordt is het onderdeel van de standaardbehandeling. Er zijn uit eerder onderzoek aanwijzingen dat patiënten met een agressieve tumor biologie mogelijk wel baat hebben bij perioperatieve systemische chemotherapie. De analyses van deze thesis in 2020 patiënten suggereren dat perioperatieve systemische chemotherapie geen invloed heeft op de incidentie van het krijgen van een intrahepatisch recidief. Perioperatieve systemische chemotherapie lijkt te leiden tot een reductie van de incidentie van longrecidieven, echter dit werd alleen gevonden in patiënten met een hoge CRS. In **hoofdstuk 5** hebben we de recidiefpatronen vergeleken tussen patiënten die zijn behandeld met HAIP chemotherapie en systemische chemotherapie of systemische chemotherapie alleen. In dit onderzoek van 2128 patiënten werd een associatie gevonden tussen een verlaging van de incidentie van intrahepatische recidieven en de behandeling met HAIP chemotherapie. Tevens werd er een hogere incidentie van longrecidieven gevonden bij patiënten die zijn behandeld met HAIP chemotherapie. Mogelijk kan dit worden verklaard doordat meer patiënten de kans hadden een eerste extrahepatisch recidief te ontwikkelen in afwezigheid van een intrahepatisch recidief. **Hoofdstuk 6** beschrijft een onderzoek over de toegevoegde waarde van HAIP chemotherapie in een groep van 374 patiënten na een resectie of ablatie van geïsoleerde intrahepatische recidieven. Het onderzoek impliceert dat adjuvante HAIP chemotherapie een verbetering van de lever-specifieke ziektevrije overleving en algehele overleving geeft. De resultaten van

deze studie zijn veelbelovend maar moeten worden bevestigd in een prospectieve studie (PUMP III, NTR NL9294).

Deel II: Klinisch onderzoek van hepatic arterial infusion pump chemotherapie

De veiligheid en haalbaarheid van adjuvante HAIP chemotherapie is onderzocht in een fase II onderzoek waarvan de resultaten zijn gepresenteerd in **hoofdstuk 7**. In totaal zijn er twintig patiënten in twee centra behandeld (Erasmus MC Kanker Instituut, Rotterdam; Antoni van Leeuwenhoek, Amsterdam). Alle patiënten werden behandeld met een maximum van 6 kuren met HAIP chemotherapie. Bij twee patiënten (10%) werden er HAIP gerelateerde postoperatieve complicaties binnen 90 dagen na implantatie geregistreerd. Beiden hebben een heroperatie ondergaan (zonder laparotomie); de eerste vanwege een verminderde infusie snelheid van de pomp en de tweede vanwege een gekantelde pomp. Alle patiënten hebben hun eerste kuur HAIP chemotherapie gekregen. In **hoofdstuk 8** is het onderzoeksprotocol van de multicenter fase III RCT (PUMP) besproken. De studie onderzoekt de effectiviteit van HAIP chemotherapie na resectie van CRLM in patiënten met een lage CRS. Er zullen in totaal 230 patiënten geïncludeerd en de eerste resultaten van dit onderzoek worden binnen enkele jaren verwacht. De onderzoekspopulatie is geselecteerd op basis van een grote retrospectieve studie van 2368 van het Memorial Sloan Kettering Cancer Center (New York, Verenigde Staten). De mediane algehele overleving was 67 maanden met HAIP chemotherapie ($n = 785$) versus 44 maanden voor patiënten die alleen een resectie ondergingen ($n = 1583$, $p < 0.001$). De overlevingswinst van HAIP chemotherapie was groter in patiënten met een lage CRS (89 maanden vs. 53 maanden, $p < 0.001$) in vergelijking met patiënten met een hoge CRS (50 maanden vs. 37 maanden, $p < 0.001$).

Deel III: Prognose, predictie en gepersonaliseerde behandeling

In **hoofdstuk 9** hebben we onderzocht of het histopathologisch groeipatroon (HGP) de effectiviteit van systemische chemotherapie na resectie van levermetastasen kan voorspellen. Veelbelovend recent onderzoek suggereert dat HGPs een belangrijke prognostische factor zijn voor patiënten met resectabele CRLM. HGPs omvatten de overgang van tumorweefsel naar normaal leverparenchym. Er zijn drie type HGPs; het desmoplastic type, waarin de tumorcellen door een desmoplastische rand worden gescheiden van het normale leverparenchym; het replacement type, waarin de tumorcellen het normale leverparenchym infiltreren lang de vasculaire structuren; en het pushing type, waarin de tumorcellen het normale leverparenchym wegdrukken. Het pushing type HGP is zeldzaam en heeft gelijke overlevings karakteristieken als het replacement type HGP. Hieronder vallen ook de mengvormen van verschillende HGP types. Samen worden de pushing, replacement en mixed HGPs types ook wel non-desmoplastic type HGP genoemd. Een eerder onderzoek heeft aangetoond dat de overleving van patiënten met een non-desmoplastic HGP slechter is dan die met een desmoplastic type HGP. Het onderzoek suggereerde ook dat de prognostische waarde van HGPs verminderd is als patiënten zijn voorbehandeld met chemotherapie voor de resectie van CRLM. Uit het onderzoek van deze thesis in 1236 patiënten lijkt het dat patiënten die niet zijn voorbehandeld met chemotherapie en een non-desmoplastic HGP hebben, baat hebben bij adjuvante systemische chemotherapie. Patiënten die voorbehandeld

zijn en patiënten met een desmoplastic HGP lijken geen baat te hebben bij adjuvante systemische chemotherapie. In **hoofdstuk 10** hebben we de resultaten beschreven van een onderzoek waarin 4112 patiënten zijn geïncludeerd, met als doel om een model te ontwikkelen om individuele 10-jaar overleving na resectie van CRLM te voorspellen op basis van patiënt-, tumor- en therapie factoren. De 10-jaars overleving was 30%. Een vereenvoudigde risicoscore is ontwikkeld waarmee patiënten in groepen kunnen worden ingedeeld met een zeer ongunstige (12%), ongunstige (24%), gemiddelde (38%) en gunstige (57%) kans op 10-jaars overleving.

References

1. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341(27):2039-48.
2. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371(9617):1007-16.
3. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14(12):1208-1215.
4. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; 352(7):734-5.
5. Ychou M, Hohenberger W, Thezenas S, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. *Annals of Oncology* 2009; 20(12):1964-1970.
6. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25(29):4575-80.
7. https://www.oncoline.nl/colorectaalcarcinoom.
8. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. *J Clin Oncol* 2017:JCO2016718346.
9. Kingham T.P.; Wei A.C.; Grünhagen D.J.; Verhoef C.; D'Angelica M.I.; Groot Koerkamp B. BFEFWFKNESEWBVPCADJAJWR. Predicting individual 10-year survival after resection of colorectal liver metastases. *Submitted* 2019.
10. Kemeny N, Conti JA, Cohen A, et al. Phase II study of hepatic arterial floxuridine, leucovorin, and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 1994; 12(11):2288-95.
11. Kemeny NE, Jarnagin WR, Capanu M, et al. Randomized phase II trial of adjuvant hepatic arterial infusion and systemic chemotherapy with or without bevacizumab in patients with resected hepatic metastases from colorectal cancer. *J Clin Oncol* 2011; 29(7):884-9.
12. Kemeny N, Jarnagin W, Gonen M, et al. Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer. *J Clin Oncol* 2003; 21(17):3303-9.

13. Kemeny N, Capanu M, D'Angelica M, et al. Phase I trial of adjuvant hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone plus systemic oxaliplatin, 5-fluorouracil and leucovorin in patients with resected liver metastases from colorectal cancer. *Ann Oncol* 2009; 20(7):1236-41.
14. D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. *Ann Surg* 2015; 261(2):353-60.
15. Pak LM, Kemeny NE, Capanu M, et al. Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential. *J Surg Oncol* 2018; 117(4):634-643.
16. Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer* 2016; 122(5):758-65.
17. Cercek A, Boerner T, Tan BR, et al. Assessment of Hepatic Arterial Infusion of Floxuridine in Combination With Systemic Gemcitabine and Oxaliplatin in Patients With Unresectable Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol* 2019.
18. Curley SA, Chase JL, Roh MS, et al. Technical considerations and complications associated with the placement of 180 implantable hepatic arterial infusion devices. *Surgery* 1993; 114(5):928-35.
19. Hohn D, Melnick J, Stagg R, et al. Biliary sclerosis in patients receiving hepatic arterial infusions of floxuridine. *J Clin Oncol* 1985; 3(1):98-102.
20. Balch CM, Urist MM. Intraarterial chemotherapy for colorectal liver metastases and hepatomas using a totally implantable drug infusion pump. *Recent Results Cancer Res* 1986; 100:234-47.
21. Haq MM, Valdes LG, Peterson DF, et al. Fibrosis of extrahepatic biliary system after continuous hepatic artery infusion of floxuridine through an implantable pump (Infusaid pump). *Cancer* 1986; 57(7):1281-3.
22. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg* 2005; 201(1):57-65.
23. Buisman FE, Grunhagen DJ, Homs MYV, et al. Adjuvant Hepatic Arterial Infusion Pump Chemotherapy After Resection of Colorectal Liver Metastases: Results of a Safety and Feasibility Study in The Netherlands. *Ann Surg Oncol* 2019.
24. Chakedis J, Beal EW, Sun S, et al. Implementation and early outcomes for a surgeon-directed hepatic arterial infusion pump program for colorectal liver metastases. *J Surg Oncol* 2018; 118(7):1065-1073.
25. Lorenz M, Muller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic

acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). *Ann Surg* 1998; 228(6):756-62.
26. https://www.esmo.org/Press-Office/Press-Releases/ESMO-Congress-anticancer-drugs-cost-Marino-Vokinger.
27. Goere D, Pignon JP, Gelli M, et al. 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* 2018; 18(1):787.
28. Kaplan DGS. A Lifesaving Pump for Cancer Patients Is Being Phased Out. *The New York Times* 2018.
29. Buisman FE, Homs MYV, Grunhagen DJ, et al. 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* 2019; 19(1):327.
30. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg* 2012; 255(3):534-9.
31. Ayez N, van der Stok EP, Grunhagen DJ, et al. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol* 2015; 41(7):859-67.
32. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. *BMC Cancer* 2014; 14:174.
33. Buisman FE, Galjart B, van der Stok EP, et al. Recurrence Patterns After Resection of Colorectal Liver Metastasis are Modified by Perioperative Systemic Chemotherapy. *World J Surg* 2019.
34. Galjart B, Nierop PMH, van der Stok EP, et al. Angiogenic desmoplastic histopathological growth pattern as a prognostic marker of good outcome in patients with colorectal liver metastases. *Angiogenesis* 2019; In Press.
35. Vermeulen PB, Colpaert C, Salgado R, et al. Liver metastases from colorectal adenocarcinomas grow in three patterns with different angiogenesis and desmoplasia. *J Pathol* 2001; 195(3):336-42.
36. van Dam PJ, van der Stok EP, Teuwen LA, et al. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 2017.
37. Huiskens J, van Gulik TM, van Lienden KP, et al. Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2015; 15:365.
38. Kemeny N, Jarnagin W, Paty P, et al. Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. *J Clin Oncol* 2005; 23(22):4888-96.

39. Kemeny N, Eid A, Stockman J, et al. Hepatic arterial infusion of floxuridine and dexamethasone plus high-dose Mitomycin C for patients with unresectable hepatic metastases from colorectal carcinoma. *J Surg Oncol* 2005; 91(2):97-101.
40. Ammori JB, Kemeny NE, Fong Y, et al. Conversion to complete resection and/or ablation using hepatic artery infusional chemotherapy in patients with unresectable liver metastases from colorectal cancer: a decade of experience at a single institution. *Ann Surg Oncol* 2013; 20(9):2901-7.
41. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2009; 27(21):3465-71.
42. Henricks LM, Lunenburg C, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol* 2018; 19(11):1459-1467.

Appendices

List of publications
Contributing authors
PhD Portfolio
Acknowledgements
About the author

List of publications

Publications in this thesis

Buisman FE, Filipe WF, Galjart B, Grünhagen DJ, Homs MYV, Moelker A, Verhoef C, Groot Koerkamp B. Adjuvant intra-arterial chemotherapy for patients with resected colorectal liver metastases: a systematic review and meta-analysis. *Accepted HPB 2021*.

Buisman FE, Filipe WF, Kemeny NE, Narayan RR, Srouji RM, Balachandran VP, Boerner T, Drebin JA, Jarnagin WR, Kingham TP, Wei AC, Grünhagen DJ, Verhoef C, Groot Koerkamp B, D'Angelica MI. Recurrence After Liver Resection of Colorectal Liver Metastases: Repeat Resection or Ablation Followed by Hepatic Arterial Infusion Pump Chemotherapy. Ann Surg Oncol 2021;28(2):808.

Buisman FE, Giardiello D, Kemeny KE, Steyerberg EW, Höppener DJ, Galjart B, Nierop PMH, Balachandran VP, Cercek A, Drebin JA, Gönen M, Jarnagin WR, Kingham TP, Vermeulen PB, Wei AC, Grünhagen DJ, Verhoef C, D'Angelica MI, Groot Koerkamp B. Predicting 10-year survival after resection of colorectal liver metastases; an international study including biomarkers and perioperative treatment. *Under review European Journal of Cancer.*

Buisman FE, Filipe WF, Kemeny NE, Narayan RR, Srouji RM, Balachandran VP, Boerner T, Drebin JA, Jarnagin WR, Kingham TP, Wei AC, Grünhagen DJ, Verhoef C, Groot Koerkamp B, D'Angelica MI. Recurrence After Liver Resection of Colorectal Liver Metastases: Repeat Resection or Ablation Followed by Hepatic Arterial Infusion Pump Chemotherapy. Ann Surg Oncol 2021;28(2):808.

Buisman FE, van der Stok EP, Galjart B, Vermeulen PB, Balachandran VP, Coebergh van den Braak RRJ, Creasy JM, Höppener DJ, Jarnagin WR, Kingham TP, Nierop PMH, Sadot E, Shia J, Groot Koerkamp B, Grünhagen DJ, D'Angelica MI, Verhoef C. Histopathological growth patterns as biomarker for adjuvant systemic chemotherapy in patients with resected colorectal liver metastases. Clin Exp Metastasis 2020;37(5):593.

Buisman FE, Galjart B, van der Stok EP, Allen PJ, Balachandran VP, Cercek A, Grünhagen DJ, Jarnagin WR, Kemeny NE, Kingham TP, Verhoef C, Groot Koerkamp B, D'Angelica MI. The impact of hepatic arterial infusion pump chemotherapy on hepatic recurrences and survival in patients with resected colorectal liver metastases. HPB 2020;22(9):1271.

Buisman FE, Galjart B, van der Stok EP, Balachandran VP, Boerner T, Drebin JA, Grünhagen DJ, Jarnagin WR, Kingham TP, Verhoef C, D'Angelica MI, Groot Koerkamp B. Recurrence patterns after resection of colorectal liver metastasis are modified by perioperative systemic chemotherapy. World J Surgery 2020;44(3):876.

Buisman FE, Grünhagen DJ, Homs MYV, Grootscholten MI, Filipe WF, Kemeny NE, Cercek A, D'Angelica MI, Donswijk ML, van Doorn L, Emmering J, Jarnagin WR, Kingham TP, Klompenhouwer EG, Kok NFM, Kuiper MC, Moelker A, Prevoo W, Versleijen MWJ, Verhoef C, Kuhlmann KFD, Groot Koerkamp B. Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases; results of a feasibility study in the Netherlands. Ann Surg Oncol 2019;26(13):4599.

Buisman FE, Homs MYV, Grünhagen DJ, Filipe WF, Bennink RJ, Besselink MGH, Borel Rinkes IHM, Bruijnen RCG, Cercek A, D'Angelica MI, van Delden OM, Donswijk ML, van Doorn L, Doornebosch PG, Emmering J, Erdmann JI, IJzerman NS, Grootscholten C, Hagendoorn J, Kemeny NE, Kingham TP, Klompenhouwer EG, Kok NFM, Koolen S, Kuhlmann KFD, Kuiper MC, Lam MGE, Mathijssen RHJ, Moelker A, Oomen-de Hoop E, Punt CJA, te Riele WW, Roodhart JML, Swijnenburg RJ, Prevoo W, Tanis PJ, Vermaas M, Versleijen MWJ, Veuger FP, Weterman MJ, Verhoef C, Groot Koerkamp B. 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 2019;19(1):327.

Other publications

Starmans MPA*, **Buisman FE***, Renckens M, Willemssen FEJA, van der Voort SR, Groot Koerkamp B, Grünhagen DJ, Niessen WJ, Vermeulen PB, Verhoef C, Visser JJ. An automatic method for distinguishing pure histopathological growth patterns of colorectal liver metastases on CT using deep learning and radiomics: a pilot study. *Accepted Clin Exp Metastasis 2020.*

Nierop PMH, Höppener DJ, **Buisman FE**, van der Stok EP, Galjart B, Balachandran VP, Jarnagin WR, Kingham TP, Shia J, Mauer M, Nordlinger B, Julie C, Groot Koerkamp B, Doekas M, Vermeulen PB, Grünhagen DJ, D'Angelica MI, Verhoef C. Preoperative systemic chemotherapy alters the histopathological growth patterns of colorectal liver metastases. J Pathol Clin Rec. 2021.

Srouji RM, Narayan RR, Boerner T, **Buisman FE**, Seier K, Gonen M, Balachandran VP, Drebin JA, Jarnagin WR, Kingham TP, Wei A, Kemeny NE, D'Angelica MI. Extrahepatic recurrence rates in patients receiving adjuvant hepatic artery infusion and systemic chemotherapy after complete resection of colorectal liver metastases. J Surg Oncol 2020;122(8):1536.

Srouji R, Narayan R, Boerner T, **Buisman FE**, Seier K, Gonen M, Balachandran VP, Drebin J, Jarnagin WR, Kingham TP, Wei A, Kemeny NE, D'Angelica MI. Addition of adjuvant hepatic artery infusion to systemic chemotherapy following resection of colorectal liver metastases is associated with reduced liver-related mortality. J Surg Oncol. 2020 Jun;121(8):1314.

Nierop PMH, Höppener DJ, van der Stok EP, Galjart B, **Buisman FE**, Balachandran VP, Jarnagin WR, Kingham TP, Allen PJ, Shia J, Vermeulen PB, Groot Koerkamp B, Grünhagen DJ, Verhoef C, D'Angelica MI. Histopathological growth patterns and positive margins after resection of colorectal liver metastases. HPB (Oxford). 2020 Jun;22(6):911.

Buisman FE, Galjart B, Buettner S, Groot Koerkamp B, Grünhagen DJ, Verhoef C. Primary tumor location and the prognosis of patients with surgically treated colorectal liver metastases: a systematic review and meta-analysis. HPB 2020;22(3):351.

Buisman FE, Homs, MYV, Grünhagen DJ, Verhoef C, Groot Koerkamp B. Adjuvant hepatic arterial infusion pump chemotherapie met resectie in vergelijking met resectie alleen voor patiënten met resectabele colorectale levermetastasen. Ned Tijdschr Oncol 2019;16:289.

Buettner S, Groot Koerkamp B, Ejaz A, **Buisman FE**, Kim Y, Margonis GA, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, Gamblin TC, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Marsh JW, IJzermans JN, Pawlik TM. The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients - A multi-institutional analysis. J Surg Oncol 2017;115(3):312.

Buisman FE, van de Berg JW, Kroon HM, Spaander MCW, Slagter C, Hauer AD, Wijnhoven BPL. Opereren of observeren van een bloedende maagtumor: overwegingen vanuit de klinische praktijk. Nederlands Tijdschrift voor Heelkunde 2016.

Buisman FE, van Gelder L, Menke-Pluymers MBE, Bisschops RHC, Plaisier PW, Westenend PJ. Non-primary breast malignancies: a single institution's experience of a diagnostic challenge with important therapeutic consequences-a retrospective study. World J Surg Oncol 2016;14(1):166.

Iordens GIT, Mahabier KC, **Buisman FE**, Schep NWL, Muradin GSR, Beenen LFM, Patka P, van Lieshout EMM, den Hartog D. The reliability and reproducibility of the Hertel classification for comminuted proximal humeral fractures compared with the Neer classification. J Orthop Sci 2016;21(5):596.

Buisman FE, de Meijer VE. Een vrouw met explosieletsel. Nederlands Tijdschrift voor Geneeskunde 2015;159:A8853.

Moerman S, **Buisman FE**, Schütte PR, Punt BJ; Repositie van supracondylaire humerus fracturen middels een tijdelijke Kirschner-draad. Nederlands Tijdschrift voor Traumatologie 2015;(2).

Contributing authors

Dr. P.J. Allen
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Dr. V.P. Balachandran
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Prof. dr. R.J. Bennink
Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, Amsterdam, the Netherlands

Prof. dr. M.G.H. Besselink, *Department of Surgery, Amsterdam University Medical Center, Amsterdam, the Netherlands*

Dr. T. Boerner
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Prof. dr. I.H.M. Borel Rinkes
Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

Prof. dr. R.C.G. Bruijnen
Department of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands

Dr. A. Cercek
Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, USA

Dr. R.R.J. Coebergh van den Braak
Department of Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

Dr. J.M. Creasy
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Prof. dr. M.I. D'Angelica
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Prof. dr. O.M. van Delden
Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, Amsterdam, the Netherlands

Dr. P.G. Doornebosch
Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands

Dr. M.L. Donswijk
Department of Nuclear Medicine, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

L. van Doorn
Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. J.A. Drebin
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Dr. J. Emmering
Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

Dr. J.I. Erdmann
Department of Surgery, Amsterdam University Medical Center, Amsterdam, the Netherlands

W.F. Filipe
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

D. Giardiello
Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands
Department of Molecular Pathology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Dr. M. Gönen
Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, USA

B. Galjart
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. Groot Koerkamp
Department of Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands

Dr. M.I. Grootscholten
Department of Medical Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Dr. D.J. Grünhagen
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. J. Hagendoorn
Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

Dr. M.Y.V. Homs
Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

D.J. Höppener
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

N.S. IJzerman
Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands
Department of Medical Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Dr. W.R. Jarnagin
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA
Dr. N.E. Kemeny
Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, USA

Dr. T.P. Kingham
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Dr. E.G. Klompenhouwer
Department of Radiology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Dr. S. Koolen
Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. N.F.M. Kok
Department of Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Dr. K.F.D. Kuhlmann
Department of Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

M.C. Kuiper
Department of Medical Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Prof. dr. M.G.E. Lam
Department of Nuclear Medicine, University Medical Center Utrecht, Utrecht, the Netherlands

Prof. dr. R.H.J. Mathijssen
Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. A. Moelker
Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

R.R. Narayan
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

P.M.H. Nierop
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. E. Oomen-de Hoop
Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. W. Prevoo
Department of Radiology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Prof. dr. C.J.A. Punt
Department of Medical Oncology, Amsterdam University Medical Center, Amsterdam, the Netherlands

Dr. W.W. te Riele
Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

Dr. J.M.L. Roodhart
Department of Medical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

E. Sadot
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

Dr. J. Shia
Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA

R.M. Srouji
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA
Prof. dr. E.W. Steyerberg
Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands
Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands

Dr. E.P. van der Stok
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. R.J. Swijnenburg
Department of Surgery, Amsterdam University Medical Center, Amsterdam, the Netherlands

Prof. dr. P.J. Tanis
Department of Surgery, Amsterdam University Medical Center, Amsterdam, the Netherlands

Prof. dr. C. Verhoef
Department of Surgery, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands

Dr. M. Vermaas
Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands

Dr. P.B. Vermeulen
Translational Cancer Research Unit, GZA Hospitals and University of Antwerp, Antwerp, Belgium

Dr. M.W.J. Versleijen
Department of Nuclear Medicine, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

F.P. Veuger
Department of Medical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

Dr. A.C. Wei
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

PhD portfolio

Name PhD student	F.E. Buisman
Erasmus MC department	Surgery
Division	Surgical Oncology
PhD Period	January 2016 – December 2019
Title thesis	Colorectal liver metastases, intra-arterial pump chemotherapy
Supervisors	Prof. dr. C. Verhoef Prof. dr. M.I. D'Angelica Dr. B. Groot Koerkamp Dr. D.J. Grünhagen
Date defense thesis	October 12, 2021

PhD Training

Oral presentations	**Year**	**ECTS**
Predicting individual 10-year survival after resection of colorectal liver metastases. 14th IHPBA World Congress (Virtual)	2020	0.5
10-jaars overleving van patiënten met colorectale levermetastasen. Johnson & Johnson Expert Meeting, Wageningen, the Netherlands	2019	0.5
Fist experience of hepatic arterial infusion chemotherapy in the Netherlands. 39th ESSO Congress, Rotterdam, the Netherlands	2019	0.5
Adjuvant hepatic arterial infusion chemotherapy after resection of colorectal liver metastases; a phase II trial. 13th E-AHPBA Congress, Amsterdam, the Netherlands	2019	0.5
PUMP pilot study – First experience of HAIP chemotherapy in the Netherlands. Surgical Oncology Conference Memorial Sloan Kettering Cancer Center, New York, USA	2019	0.5
Histopathological growth patterns as a guide for adjuvant systemic chemotherapy in patients with resected colorectal liver metastases. 38th ESSO Congress, Budapest, Hungary	2018	0.5
Recurrence rate and patterns with and without perioperative systemic chemotherapy after resection of colorectal liver metastases. 13th IHPBA World Congress, Geneva, Switzerland	2018	0.5
Recurrence rate and pattern after resection of colorectal liver metastases with and without hepatic arterial infusion chemotherapy. 13th IHPBA World Congress, Geneva, Switzerland	2018	0.5

Recurrence patterns after resection of colorectal liver metastases. NVvH Chirurgendagen, Veldhoven, the Netherlands	2018	0.5
De PUMP trial, intra-arteriële chemotherapie voor patiënten met uitzaaiingen van darmkanker in de lever. NVvOD Scholingsdag, Rotterdam, the Netherlands	2018	0.5
Histopathological growth patterns: A potential biomarker for systemic chemotherapy in patients with colorectal liver metastases. Science Day Department of Surgery Erasmus MC, Rotterdam, the Netherlands	2018	0.5
Histopathological growth patterns in patients with colorectal liver metastases. NVvH, Chirurgendagen, Veldhoven, the Netherlands	2017	0.5

Poster presentations	**Year**	**ECTS**
Primary tumor location in the prognosis after resection of colorectal liver metastases: a systematic review and meta-analysis. 38th ESSO Congress, Budapest, Hungary	2018	0.5

Courses	**Year**	**ECTS**
NIHES Msc Clinical Epidemiology	2017-2019	70.0
Workshop Hepatic Arterial Infusion Pump chemotherapy, Memorial Sloan Kettering Cancer Center, New York, USA	2018	0.6
Workshop Hepatic Arterial Infusion Pump chemotherapy, Memorial Sloan Kettering Cancer Center, New York, USA	2017	0.6
OpenClinica Training	2018	0.5
BROK (Basiscursus regelgeving Klinisch Onderzoek, NFU)	2016	1.5
Research Integrity Erasmus MC, Rotterdam, the Netherlands	2016	0.3

Teaching	**Year**	**ECTS**
Supervision Master thesis (Sanne Hazen)	2018-2019	2.0
Several hands-on PUMP Medical Oncology workshops	2017-2018	1.0
Several hands-on PUMP Surgery workshops	2017-2018	1.0

(Inter)national conferences	**Year**	**ECTS**
14th IHPBA World Congress (Virtual)	2020	0.3
39th ESSO Congress, Rotterdam, the Netherlands	2019	0.9
13th E-AHPBA Congress, Amsterdam, the Netherlands	2019	1.2
38th ESSO Congress, Budapest, Hungary	2018	0.9
13th IHPBA World Congress, Geneva, Switzerland	2018	1.2
Liver Metastases Research Network, Montreal, Canada	2018	0.6
NVvH Chirurgendagen, Veldhoven, the Netherlands	2018	0.6
Liver metastases Research network, Rotterdam, the Netherlands	2017	0.6
12th E-AHPBA Congress, Mainz, Germany	2017	1.2
NVvH Chirurgendagen, Veldhoven, the Netherlands	2017	0.6
8th European Multidisciplinary Colorectal Cancer Congress, Amsterdam, the Netherlands	2016	0.9
NVvH Chirurgendagen, Veldhoven, the Netherlands	2016	0.6

Other	**Year**	**ECTS**
Organising committee Liver Metastases Research Network congress	2017	2.0

Acknowledgements

About the author

Florian Eduard Buisman was born on February 25th 1989 in Schiedam, the Netherlands, as the second son in a family of four. He grew up in Schiedam where he completed both elementary and high school. He joined medical school in 2007 at the Erasmus University Medical Center in Rotterdam, and started his medical career as a surgical resident at the Erasmus University Medical Center after obtaining his medical degree. In 2016, he started as a PhD student at the division of Surgical Oncology of the Erasmus MC Cancer Institute (prof. dr. C. Verhoef, dr. B. Groot Koerkamp, dr. D.J. Grünhagen, prof. dr. M.I. D'Angelica). His PhD focused on introducing and implementing hepatic arterial infusion pump chemotherapy in the Netherlands. In 2019, he obtained his master's degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences, Rotterdam. He completed a research fellowship of six months at the department of Surgery (Hepatopancreatobiliary division, program director prof. dr. M.I. D'Angelica) of the Memorial Sloan Kettering Cancer Center (New York, NY, USA) in 2019. The results of his PhD research have been summarized in this thesis. In 2020 he started his surgery residency training at the IJsselland Hospital, Capelle aan den IJssel (dr. P.G. Doornebosch).