


STUDY PROTOCOL

Open Access



Hepatic arterial infusion in combination with systemic chemotherapy in patients with hepatic metastasis from colorectal cancer: a randomized phase II study – (NCT05103020) – study protocol

Ji Su Kim^{1†}, Hyunwook Kim^{2†}, Seo Young Lee^{3†}, Yoon Dae Han⁴, Kichang Han⁵, Byung Soh Min⁴, Man-Deuk Kim⁵, Jong Yun Won⁵, Seung-Hoon Beom², Sang Joon Shin², Han Sang Kim^{2,6*†} , Dai Hoon Han^{7*†} and Joong Bae Ahn^{2*†}

Abstract

Background Although 80% of patients with metastatic colorectal cancer (CRC) experience liver metastases, only 10–25% undergo resection at the time of diagnosis. Even in initially unresectable conditions, if appropriate treatment is provided, such as surgical conversion through a combination of hepatic arterial infusion (HAI) chemotherapy and systemic chemotherapy (sys-CT), better overall survival can be expected. Therefore, this study aims to evaluate the efficacy of HAI oxaliplatin in combination with sys-CT plus targeted therapy in patients with unresectable CRC with liver-only metastasis.

Methods This is a single-center, randomized, open-label phase II trial (NCT05103020). Patients with untreated CRC, who have liver-only metastases and for whom liver resection is potentially possible but deemed infeasible at the time of initial diagnosis by a multidisciplinary team, will be eligible. Patients will be randomly assigned in a 1:1 ratio to either the combined HAI oxaliplatin and modified systemic 5-fluorouracil, folinic acid, and irinotecan (FOLFIRI) plus targeted therapy group or the systemic FOLFIRI plus targeted therapy group. Both regimens will be repeated every 2 weeks for a total of 12 cycles. The primary objective of this study is to compare the rate of conversion to liver resection. The surgical conversion rate is expected to increase by 25% with HAI oxaliplatin in combination with sys-CT plus targeted therapy (40% in the experimental arm versus 15% in the control arm) (power, 80%; two-sided alpha-risk, 5%). The secondary objectives include overall survival, progression-free survival, and objective response rate.

[†]Ji Su Kim, Hyunwook Kim and Seo Young Lee are share first authorship.

[†]Han Sang Kim, Dai Hoon Han and Joong Bae are share senior authorship.

*Correspondence:

Han Sang Kim
modeerfhs@yuhs.ac
Dai Hoon Han
DHHAN@yuhs.ac
Joong Bae Ahn
vvsww513@yuhs.ac

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Discussion This is the first randomized controlled trial to investigate the efficacy of HAI oxaliplatin in combination with sys-CT plus targeted therapy as first-line treatment from the initial diagnosis in patients with unresectable CRC with liver-only metastasis, aiming to significantly increase the surgical conversion rate.

Trial registration ClinicalTrials.gov, (NCT05103020). Trial registration date: November 2, 2021.

Keywords Colon cancer, Liver-only metastasis, Liver resection, Hepatic arterial infusion, Oxaliplatin, Randomized trial

Background

The liver is the most common site of metastasis in patients with colorectal cancer (CRC). Approximately 80% of patients with stage IV disease experience liver metastasis. Of these, approximately 40% experience metastasis that is only limited to the liver [1, 2]. However, only 15–25% of patients present with resectable colorectal liver metastasis (CRLM) at the time of diagnosis [3, 4]. If all liver metastases are completely resected, then the 5-year survival rate of these patients may exceed 50% [5, 6]. Furthermore, some patients may even be cured during the long-term follow-up, with a reported cure rate of approximately 20% [5].

Conversion to surgery in patients with unresectable CRLM after systemic chemotherapy

Systemic chemotherapy (sys-CT) has been employed as neoadjuvant chemotherapy to help patients who cannot undergo liver resection at the time of diagnosis to become eligible candidates for surgery. According to a previous study, the surgical conversion rate ranges from 6 to 38%, depending on the type and duration of sys-CT and the anatomical extent of the liver metastases [7]. Several trials involving the combination of systemic chemotherapeutics with or without targeted therapies have demonstrated the downstaging of CRLM patients from initially inoperable to potentially resectable, and it was found that the objective response rate correlates with resectability [8–10]. R0 resection was possible in 19% of 196 patients with liver metastases of CRC, in whom liver resection is considered infeasible, following treatment with 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI). The median overall survival (OS) was 40 months, the 5-year disease-free survival rate was 29%, and the 5-year and 8-year survival rates were 42% and 33%, respectively [11].

Hepatic arterial infusion chemotherapy

Hepatic arterial infusion (HAI) is a treatment method in which an interventional radiologist or surgeon inserts a port into the gastroduodenal artery, allowing direct delivery of anticancer therapeutics into the liver. Several studies have employed HAI to treat metastatic liver cancers because these lesions receive their primary vascular

supply from the gastroduodenal artery. As most chemotherapeutic agents used in HAI undergo direct liver metabolism, they are expected to present a lower risk of systemic exposure and toxicity compared to those used in sys-CT protocols [12].

Fast-metabolized fluorodeoxyuridine (FUDR), 5-FU, mitomycin-C, and oxaliplatin are also being investigated for their potential use in the HAI technique [13–16]. FUDR has been widely investigated, but its routine implementation in clinical practice is hampered by certain constraints, such as the need for a 14-day continuous infusion via a pump and the inherent risk of biliary toxicity, which is unexpectedly increased with bevacizumab [17]. HAI oxaliplatin is known to accumulate in a higher concentration in liver metastases than in normal parenchyma [18], only requires a 2-h infusion time, and has a more favorable toxicity profile with reduced biliary toxicity. Moreover, even in later treatment stages, HAI oxaliplatin has shown a promising conversion rate of approximately 25%. Importantly, it has also proven effective in cases that showed resistance to systemic oxaliplatin [16, 19, 20]. Furthermore, HAI treatment is known to be more effective when the number of prior sys-CT lines are less than two [16, 21].

Combined treatment with HAI chemotherapy and sys-CT

To maximize the efficacy of HAI chemotherapy, it is essential to find the optimal sys-CT combination. Previous studies have shown that the surgical conversion rate increased to 25–47% and OS improved when HAI and sys-CT were used in combination, even in patients initially diagnosed with unresectable conditions [22]. However, contrasting findings have also been reported [23, 24]. Therefore, additional prospective trials are necessary to clarify these discrepancies and establish more definitive guidelines for the use of HAI treatment. At present, the SULTAN-PRODIGE53 (NCT03164655), a randomized phase II study, is investigating the intensified treatment combination of HAI oxaliplatin and systemic FOLFIRI plus targeted therapy compared to sys-CT alone in CRLM patients who remain non-resectable after 2–6 months of first-line induction sys-CT [25].

In order to optimize the efficacy of HAI treatment and maximize the surgical conversion rate, it is essential to investigate the utility of HAI in conjunction with

sys-CT, starting from the initial induction of chemotherapy. However, till date, no research has been conducted on this aspect. Therefore, this study aims to evaluate the concurrent use of HAI oxaliplatin and sys-CT at the time of initial diagnosis in patients with CRLM. The primary goal is to maximize the conversion rate to surgery in a shorter period with less systemic toxicity by comparing it with that of the existing irinotecan-based standard treatment.

Methods/design

Patients and study design

This study is designed as an open-label, single-center, randomized phase II clinical trial to compare and evaluate the efficacy of the combination of HAI oxaliplatin with sys-CT (FOLFIRI) plus targeted therapy (bevacizumab or cetuximab) in treatment-naïve patients with CRC with potentially resectable liver-only metastases. The study flowchart is presented in Fig. 1.

The eligibility criteria will be as follows: (1) patients aged at least 19 years, (2) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and (3) life expectancy of at least 3 months. Unsuitability for liver resection will be ascertained by a multidisciplinary team (surgeon, radiologist, interventional radiologist, and oncologist) based on criteria enumerated in Table 1. Patients will be assigned randomly at a central institution to one of the two arms in a 1:1 ratio using the stratified permuted block randomization approach, with the ECOG PS and prior adjuvant chemotherapy experience as the stratification factors, viz. 2-h HAI oxaliplatin 100 mg/m² and a systemic modified FOLFIRI regimen (1.5-h intravenous irinotecan 180 mg/m² on day 1, 2-h intravenous leucovorin 400 mg/m² followed by 46-h intravenous 5-FU 2400 mg/m² on day 1 without 5-FU bolus) plus targeted therapy (2-h intravenous cetuximab 500 mg/m² or 30-min intravenous bevacizumab 5 mg/kg) (experimental arm), or systemic FOLFIRI (1.5-h intravenous irinotecan 180 mg/m² on day 1, intravenous 5-FU bolus 400 mg/m², and 2-h intravenous leucovorin 400 mg/m² followed by 46-h intravenous 5-FU 2400 mg/m² on day 1) plus targeted therapy (2-h IV cetuximab 500 mg/m² or 30-min intravenous bevacizumab 5 mg/kg) (control arm). Both regimens will be repeated every 2 weeks for a total of at least 4 cycles, but no more than 12 cycles, depending on the circumstances. Treatment will continue until the cancer is deemed resectable, the cancer progresses, drug toxicity occurs, or the patient refuses further treatment. After 12 cycles, the decision will be made by the researcher on whether to proceed with surgery or to continue with palliative chemotherapy. For those in the experimental arm, 5-FU plus leucovorin is to be continued at least until disease progression,

intolerable side effects, or patient withdrawal of consent, even if it is difficult to maintain the HAI treatment due to the side-effects.

A HAI catheter will be implanted by an interventional radiologist. Access to the HAI catheter is restricted to medical professionals who are skilled in using the HAI catheter and are knowledgeable about and trained in HAI chemotherapy. Its condition and function will be examined before each use.

Endpoints and assessments

The primary study objective is the rate of conversion to liver resection. The secondary objectives include OS, progression-free survival, and objective response rate.

Carcinoembryonic antigen testing, chest radiography, computed tomography/magnetic resonance imaging, and tumor assessment are to be conducted every 8 weeks. Follow-up will be conducted every 6 months for up to 4 years following randomization.

Statistical considerations and analysis plan

We expect a gain of 25% of patients who will be converted to surgery from chemotherapy (40% in the experimental arm versus 15% in the control arm; power, 80%; two-sided alpha-risk, 5%). Overall, we aim to enroll a total of 108 participants (54 in each arm), assuming a drop-out rate of 10%.

A major statistical analysis of treatment efficacy will be performed on the intention-to-treat population. Categorical data will be summarized in tables showing the frequency and corresponding proportions for each treatment group. Serial data will be summarized by treatment group using frequency, mean, standard deviation, median (if applicable), minimum, and maximum values. The descriptive analysis will be summarized for each treatment group and as a whole, with a description of the characteristics of the pretreatment phase. Hazard ratio and 95% confidence interval will be calculated according to the Cox proportional-hazard model, and the survival curve will be calculated according to the Kaplan–Meier method. Safety will be assessed based on analysis of adverse events and findings from standard clinical routine laboratory testing.

Toxicity monitoring

Clinical and laboratory adverse events/symptoms will be graded according to Common terminology criteria for adverse events version 4.03 [26]. Liver enzymes (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and bilirubin) will be closely monitored to evaluate liver and biliary toxicities. Once a dose reduction is made, no subsequent dose increase is permitted. However, if it is determined that the toxicity is related to

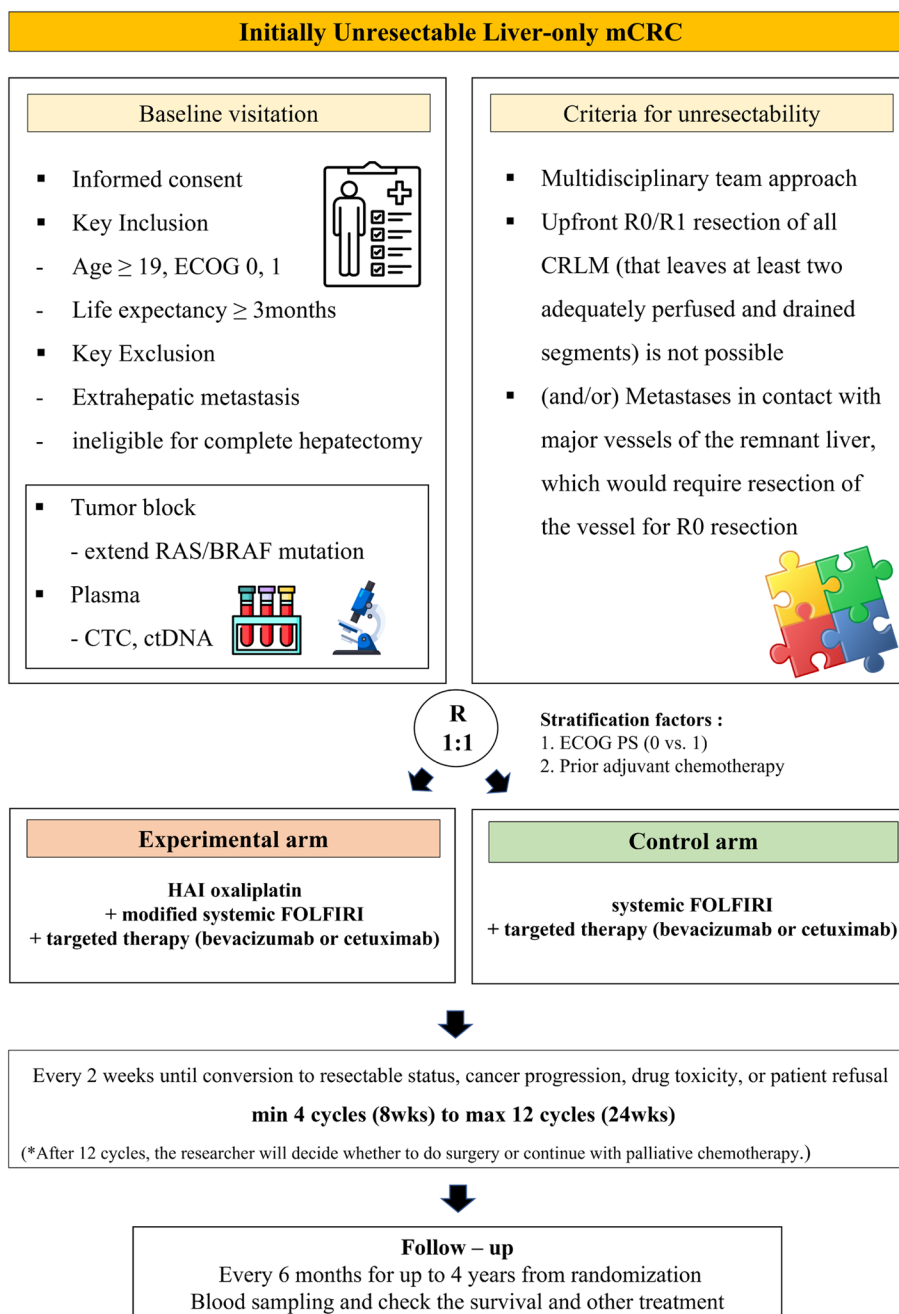


Fig. 1 Flow diagram of the trial. A total of 108 treatment-naïve patients with colon cancer with liver-only metastasis will be randomized in a ratio of 1:1 to the HAI oxaliplatin combined with systemic modified FOLFIRI plus targeted therapy group, or the systemic FOLFIRI plus targeted therapy group. HAI Hepatic artery infusion, 5-FU: 5-fluorouracil, CEA Carcinoembryonic antigen, CT Computed tomography, MRI Magnetic resonance imaging, FOLFIRI: 5-fluorouracil, folinic acid and irinotecan, ECOG Eastern cooperative oncology group, PS Performance status

the test drug, the investigator may reduce or discontinue the test drug at the discretion of the investigator by referring to the dose adjustment recommendation.

Granulocyte colony stimulating factor is not recommended as a primary prophylaxis. However, it can be used for secondary prevention in cases of prior febrile

neutropenia, grade 4 neutropenia lasting for more than 5 days, or if the planned treatment is delayed by two or more times due to neutropenia.

If a patient undergoing HAI oxaliplatin treatment reports abdominal pain or catheter-related discomfort, it would be necessary to inspect the HAI catheter for

Table 1 Key Inclusion and exclusion criteria**Inclusion criteria**

- Age \geq 19 years
- ECOG PS \leq 1
- Advanced colorectal cancer (stage IV) with histologically proven unresectable liver-only metastases
- Evaluation of unresectable liver metastases based on imaging tests (CT/MRI) by a multidisciplinary team (including surgeons, radiologists, interventional radiologists, and medical oncologists)
- Criteria for unresectability
 - ° Upfront R0/R1 resection of all CRLM (leaves at least two adequately perfused and drained segments) is not possible
 - ° And/or metastases in contact with major vessels of the remnant liver, which would require resection of the vessel for R0 resection (i.e., tumor involvement of the main right and left portal veins, three main hepatic veins, or retrohepatic vena cava)
- No prior chemotherapy
- Adequate organ function
 - ° ANC \geq 1.5×10^9 /L
 - ° PLT \geq 100×10^9 /L
 - ° Total bilirubin \leq $1.5 \times$ ULN
 - ° Urine dipstick of proteinuria $< 2+$ (if $\geq 2+$, ≤ 1 g of protein/24 h)
- Life expectancy \geq 3 months

° Hb \geq 9.0 g/dL (including transfusion)° AST/ALT \leq $5 \times$ ULN, ALP \leq $5 \times$ ULN° CrCl \geq 45 mg/min (Cockcroft-Gault formula)**Exclusion criteria**

- Anatomically or medically not suitable for complete surgical resection
 - ° Two or more tumors in all hepatic segments
 - ° Bilobar liver metastases and more than 3 lesions (> 3 cm) in the future remnant liver
 - ° Bilobar liver metastases and liver disease extending to $> 50\%$ of the organ
- Extrahepatic metastasis
- Peripheral neuropathy \geq grade 2 (CTCAE ver.4.03)
- Any other condition that may interfere with patients' participation/evaluation in the study

ANC Absolute neutrophil count, Hb Hemoglobin, PLT Platelet, AST Aspartate aminotransferase, ALT Alanine aminotransferase, ALP Alkaline phosphatase, CrCl Creatinine clearance, CT Computed tomography, MRI Magnetic resonance imaging, ECOG Eastern Cooperative Oncology Group, PS Performance status, CRLM Colorectal liver metastasis, CTCAE Common terminology criteria for adverse events, ULN Upper limit of normal

potential issues, such as malfunction, infection, or leakage. If such problems are identified, the investigator should consider removing and reinserting the catheter at his or her discretion.

Ancillary study: biomarker analysis

Transitional research investigates the correlation between the maximum tumor shrinkage rate and the variation of circulating tumor DNA (ctDNA) concentration, pre- and post-planned treatment. The relationship between the changes in circulating tumor cells and progression-free survival will also be explored. In addition, the concordance rate of mutation identification in formalin-fixed paraffin-embedded samples and ctDNA will be compared and assessed to discover KRAS exon 2 (G12X, G13X), exon 3 (Q61X), NRAS exon 2 (G12X), exon 3 (Q61X), and BRAF exon 15 (V600E) mutations.

Data collection, management, and monitoring

All trial data will be collected and managed in papers and also maintained and monitored by the principal investigator at Yonsei Cancer Center. We estimated the patient accrual and study duration to take 2 and 4 years, respectively.

Discussion

R0 resection is critical for the long-term survival of patients with stage IV CRC. Considering this might be the patient's last opportunity for a cure, finding a more effective treatment strategy is crucial. Such a strategy could allow curative aim surgery to be performed on patients initially considered unsuitable for liver resection at diagnosis. The group treated with systemic bevacizumab-FOLFOXIRI in the OLIVIA trial [9] not only demonstrated higher response rates, but also a higher resection rate of 61% (95% CI, 45–76%) and an R0 resection rate of 49% when compared to those of the bevacizumab-mFOLFOX-6 group. However, more than 95% of patients experienced toxicity events of grade 3 or higher. As a result, there is an urgent need to continue efforts to develop more tolerable and safer treatment methods. In this regard, the therapeutic regimen of HAI oxaliplatin combined with modified FOLFIRI plus targeted therapy is thought to reflect these requirements well. However, there are also several limitations to consider. To administer HAI chemotherapy, an invasive procedure for the insertion of an intra-arterial port is necessary. There is also a risk of liver injury due to the HAI catheter tip,

which requires caution. Moreover, the complexity of these procedures makes widespread adoption across all institutions difficult.

Another important point in this study is the need to determine the possibility of liver resection in a timely manner while receiving systemic treatment. A multi-disciplinary approach is required to evaluate the likelihood of resection, taking into account the condition of the tumor before and after chemotherapy, as well as the performance status of the patient, environment, and life expectancy. To conduct this evaluation in a comprehensive manner, surgeons, radiologists, and physicians should jointly review every radiologic image for response evaluation. Most importantly, the surgeon's perspective is particularly significant in this context.

This is the first randomized controlled trial to investigate HAI oxaliplatin in combination with sys-CT plus targeted therapy as first-line treatment from the initial diagnosis in patients with CRC with potentially resectable liver-only metastasis. The primary objective of this trial is to significantly increase the surgical conversion rate. We plan to include 108 patients, and the recruitment period and observation period are 2 years each. While direct comparison with the ongoing SULTAN-PRODIGE53 study (NCT03164655) [16] is challenging, the results from both studies will provide valuable insights into the role and optimal application timing of HAI treatments. Further research is necessary to determine which patients will benefit the most from HAI combination, as well as to ascertain the optimal sys-CT and targeted agent combination regimen and the ideal duration of post-operative systemic therapy for maintaining a disease-free status.

Abbreviations

CRC	Colorectal cancer
HAI	Hepatic arterial infusion
5-FU	5-Fluorouracil
CRLM	Colorectal liver metastasis
ctDNA	Circulating tumor DNA
ECOG	Eastern cooperative oncology group
PS	Performance status
FOLFIRI	5-Fluorouracil, folinic acid, and irinotecan
FUDR	Fluorodeoxyuridine
OS	Overall survival
sys-CT	Systemic chemotherapy
FOLFOXIRI	5-Fluorouracil, leucovorin, oxaliplatin, and irinotecan

Acknowledgements

None.

Authors' contributions

JSK, HK, HSK drafted this manuscript. SYL, YDH, KH, BSM, MDK, JYW, SHB, SJS, DHH and BJA contributed to the study design. HK, SYL, HSK, SHB, SJS, and BJA will conduct the translational research. HSK, DHH, and JBA are the principal investigators of the study. JSK, HK, SYL, YDH, KH, BSM, MDK, JYW, SHB, SJS, HSK, DHH, and BJA contributed to the study and have read and approved the final manuscript.

Funding

This study was supported by a Severance Hospital Research fund for Clinical excellence (SHRC) (C-2021-0002 to D.H.H.), and a new faculty research seed money grant of Yonsei University College of Medicine (2022-32-0062 to D.H.H.). This study was also supported in part by the National Research Foundation of Korea (NRF) grant, funded by the Korea government Ministry of Science and ICT (MSIT) (No. 2022R1A2C4001879 to H.S.K.).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

All participating authors follow Good Clinical Practice, and the study will be conducted according to the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Boards of Severance Hospital (IRB 4-2021-0034). All patients enrolled provided written informed consent.

Consent for publication

This study does not contain individual data of person.

Competing interests

The authors declare no competing interests.

Author details

¹Division of Hepatobiliary and Pancreas Surgery, Incheon St. Mary's Hospital, The Catholic University College of Medicine, Incheon, Korea. ²Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-Ro, Seodaemun-Gu, Seoul 03722, South Korea. ³Department of Medical Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. ⁴Department of Colorectal Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. ⁵Department of Radiology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. ⁶Graduate School of Medical Science, Brain Korea 21 Project, Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea. ⁷Department of Hepatobiliary and Pancreatic Surgery, Severance Hospital, Yonsei University College of Medicine, 50 Yonsei-Ro, Seodaemun-Gu, Seoul 03722, South Korea.

Received: 20 September 2022 Accepted: 16 June 2023

Published online: 22 July 2023

References

- Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg*. 1995;19(1):59–71.
- Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am*. 2003;12(1):165–92 xi.
- Bismuth H, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, Majno P, Engerran L. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg*. 1996;224(4):509–20 discussion 520–502.
- Devaud N, Kanji ZS, Dhani N, Grant RC, Shoushtari H, Serrano PE, Nanji S, Greig PD, McGilvray I, Moulton CA, et al. Liver resection after chemotherapy and tumour downsizing in patients with initially unresectable colorectal cancer liver metastases. *HPB (Oxford)*. 2014;16(5):475–80.
- Tomlinson JS, Jarnagin WR, Dematteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M. Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure. *J Clin Oncol*. 2007;25(29):4575–80.
- De Haas RJ, Wicherts DA, Salloum C, Andreani P, Sotirov D, Adam R, Castaing D, Azoulay D. Long-term outcomes after hepatic resection for colorectal metastases in young patients. *Cancer*. 2009;116(3):647–58.
- Kemeny N. The management of resectable and unresectable liver metastases from colorectal cancer. *Curr Opin Oncol*. 2010;22(4):364–73.

8. Folprecht G, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol.* 2005;16(8):1311–9.
9. Gruenberger T, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S, Lasserre S, Hermann F, Waterkamp D, Adam R. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol.* 2015;26(4):702–8.
10. Ye L-C, Liu T-S, Ren L, Wei Y, Zhu D-X, Zai S-Y, Ye Q-H, Yu Y, Xu B, Qin X-Y, et al. Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients With *KRAS* Wild-Type Unresectable Colorectal Liver-Limited Metastases. *J Clin Oncol.* 2013;31(16):1931–8.
11. Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, Brunetti IM, Ferraldeschi R, Naso G, Filipponi F, 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.
12. Zervoudakis A, Boucher T, Kemeny NE. Treatment Options in Colorectal Liver Metastases: Hepatic Arterial Infusion. *Visc Med.* 2017;33(1):47–53.
13. Chang AE, Schneider PD, Sugarbaker PH, Simpson C, Culnane M, Steinberg SM. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg.* 1987;206(6):685–93.
14. Hohn DC, Stagg RJ, Friedman MA, Hannigan JF Jr, Rayner A, Ignoffo RJ, Acord P, Lewis BJ. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol.* 1989;7(11):1646–54.
15. Fiorentini G, Rossi S, Dentico P, Meucci F, Bonechi F, Bernardeschi P, Cantore M, Guadagni S, De Simone M. Oxaliplatin hepatic arterial infusion chemotherapy for hepatic metastases from colorectal cancer: a phase I-II clinical study. *Anticancer Res.* 2004;24(3b):2093–6.
16. Boilève A, De Cuyper A, Larive A, Mahjoubi L, Najdawi M, Tazdait M, Gelli M, Tselikas L, Smolenschi C, Malka D, et al. Hepatic arterial infusion of oxaliplatin plus systemic chemotherapy and targeted therapy for unresectable colorectal liver metastases. *Eur J Cancer.* 2020;138:89–98.
17. Kemeny NE, Jarnagin WR, Capanu M, Fong Y, Gewirtz AN, Dematteo RP, D'Angelica M. 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.
18. Dzodic R, Gomez-Abuin G, Rougier P, Bonnay M, Ardouin P, Gouyette A, Rixe O, Ducreux M, Munck JN. 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.
19. Ducreux M, Ychou M, Laplanche A, Gamelin E, Lasser P, Hussein F, Quenet F, Viret F, Jacob J-H, Boige V, et al. Hepatic Arterial Oxaliplatin Infusion Plus Intravenous Chemotherapy in Colorectal Cancer With Inoperable Hepatic Metastases: A Trial of the Gastrointestinal Group of the Fédération Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol.* 2005;23(22):4881–7.
20. Boige V, Malka D, Elias D, Castaing M, De Baere T, Goere D, Dromain C, Pocard M, Ducreux M. Hepatic Arterial Infusion of Oxaliplatin and Intravenous LV5FU2 in Unresectable Liver Metastases from Colorectal Cancer after Systemic Chemotherapy Failure. *Ann Surg Oncol.* 2008;15(1):219–26.
21. Lim A, Le Sourd S, Senellart H, Luet D, Douane F, Perret C, Bouvier A, Métairie S, Cauchin E, Rougier P, et al. Hepatic Arterial Infusion Chemotherapy for Unresectable Liver Metastases of Colorectal Cancer: A Multi-center Retrospective Study. *Clin Colorectal Cancer.* 2017;16(4):308–15.
22. Lewis HL, Bloomston M. Hepatic Artery Infusional Chemotherapy. *Surg Clin North Am.* 2016;96(2):341–55.
23. Cercak A, Boucher TM, Gluskin JS, Aguiló A, Chou JF, Connell LC, Capanu M, Reidy-Lagunes D, D'Angelica M, Kemeny NE. Response rates of hepatic arterial infusion pump therapy in patients with metastatic colorectal cancer liver metastases refractory to all standard chemotherapies. *J Surg Oncol.* 2016;114(6):655–63.
24. Tsimberidou AM, Leick MB, Lim J, Fu S, Wheler J, Piha-Paul SA, Hong D, Falchook GS, Naing A, Subbiah IM, et al. Dose-finding study of hepatic arterial infusion of oxaliplatin-based treatment in patients with advanced solid tumors metastatic to the liver. *Cancer Chemother Pharmacol.* 2013;71(2):389–97.
25. Boilève A, Maillard A, Wagner M, Dromain C, Laurent C, Dupont Pierre E, Le Sourd S, Audemar F, Ulsakarya A, Guerin-Meyer V, et al. Treatment intensification with hepatic arterial infusion chemotherapy in patients with liver-only colorectal metastases still unresectable after systemic induction chemotherapy - a randomized phase II study – SULTAN UCGI 30/PRODIGE 53 (NCT03164655)- study protocol. *BMC Cancer.* 2020;20(1):74.
26. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2010.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

