

Hepatic Arterial Infusion Oxaliplatin Plus Oral S-1 Chemotherapy in Gastric Cancer with Unresectable Liver Metastases: A Case Series and Literature Review

This article was published in the following Dove Press journal:
Cancer Management and Research

Kangxin Wang^{1,2,*}

Xuebin Zhang^{3,*}

Jia Wei¹

Yiwen Xu⁴

Qin Liu¹

Jiaqi Xie¹

Lihua Yuan^{1,3}

Zhichen Sun¹

Siyi Tan¹

Lianru Zhang¹

Baorui Liu¹

Yang Yang¹

¹The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing 210008, People's Republic of China;

²Department of Oncology, Nanjing Pukou Central Hospital, Nanjing 211800, People's Republic of China; ³Department of Radiology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing 210008, People's Republic of China; ⁴The First Medical School of Nanjing Medical University, Nanjing 210000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yang Yang
The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, 321 Zhongshan Road, Nanjing 210008, People's Republic of China
Tel +86-18602568379
Fax +86-25-83317016
Email wing_young7@hotmail.com

Objective: The use of hepatic artery infusion (HAI) as a regional therapy against liver metastasis has rarely been reported in gastric cancer. This study aimed to evaluate the efficacy and safety of HAI oxaliplatin plus oral S-1 chemotherapy in first-line palliative therapy for gastric cancer with multiple liver metastases (GCLM).

Methods: We reviewed the records of five patients with GCLM who received HAI oxaliplatin (70–80 mg/m² 2 hrs d1,15) administered via a port-catheter system and S-1 with oral (35–40 mg/m² twice daily for d1-14, 28 days for one cycle). Follow-up examination and efficacy evaluation were executed periodically.

Results: Until the 4th cycle response evaluation, the local effective rate and control rate were 40% and 80%, respectively; only one patient developed progression. HAI chemotherapy had a better local control against liver metastases (median progression-free survival: hepatic, 8.8 months vs. extrahepatic, 6.2 months), accompanied by less systemic toxicity, decreased tumour markers and symptomatic relief.

Conclusion: HAI oxaliplatin plus oral S-1 chemotherapy can be considered as a new choice of first-line treatment for GCLM, which is also a good approach for controlling extrahepatic lesions with less adverse events.

Keywords: gastric cancer with multiple liver metastases, nonresectional regional therapy, hepatic arterial infusion, port-catheter system, response evaluation, adverse events

Introduction

Gastric cancer is one of the most common cancers and the third leading cause of cancer-related death worldwide.¹ The liver is a common metastatic site for advanced gastric cancer as a result of blood metastasis via portal circulation, which occurs in approximately 30% of patients.^{2–4} Gastric cancer with multiple liver metastases (GCLM) represents a systemic disease with synchronous or metachronous abdominal lymph node metastases or direct tumour invasions of other organs.^{5–8} Controlling liver metastases is extremely important to improve the prognosis for patients with advanced gastric cancer. Traditionally, systemic chemotherapy with oxaliplatin and S-1 was recognized as the standard treatment,⁹ however, the median progression-free survival (PFS) of metastatic gastric cancer patients treated by standard systemic chemotherapy was only 5.0–6.5 months, which seems to be unsatisfactory. In addition, the systemic toxicity of chemotherapy is common, and limited dosage after multi-line anticancer

drugs is not enough to achieve an effective serum drug concentration against liver metastases.^{3–110}

Currently, advances in vascular interventional radiology make it easy to better control GCLM. Hepatic arterial infusion (HAI) chemotherapy is an important tumour interventional therapy, and it is also a crucial way to ensure that chemotherapy can achieve a maximum anticancer effect for the local control of cancer without much systemic toxicity.^{14–17} Recently, Seki et al¹⁸ reported that HAI chemotherapy using 5-fluorouracil, epirubicin, and mitomycin C (FEM) induced significant curative effects in GCLM after the failure of systemic S-1 plus cisplatin. Furthermore, Fukami et al¹⁹ also demonstrated that adjuvant HAI chemotherapy after hemihepatectomy for GCLM could be helpful for preventing remnant liver recurrence and prolonging survival time. Thus, HAI chemotherapy may play an important role in early intervention. However, due to the existence of extrahepatic lesions, HAI chemotherapy should be combined with other systemic treatments to improve the overall response rate. To our knowledge, there are few clinical trials that apply HAI plus systemic chemotherapy in a first-line setting. Here, we report a case series of GCLM using this combination mode in first-line palliative chemotherapy, which shows initial success in gaining local tumour control, maintaining function and improving life quality.

Materials and Methods

Population

Five gastric cancer patients with multiple liver metastases were admitted to the Comprehensive Cancer Centre of Drum Tower Hospital and treated with HAI oxaliplatin infusion plus oral S-1 chemotherapy between January 2018 and February 2019. The ethics committee of Drum Tower Hospital approved our study before therapy (No.2014-020-02). Informed consent for all patients was obtained before treatment. The clinical characteristics and outcomes of the patients are listed in Table 1.

Eligibility Criteria

(1) Pathologically confirmed gastric adenocarcinoma; (2) Multiple liver metastases, which were assessed as unresectable by multidisciplinary team; (3) Eastern Cooperative Oncology Group (ECOG) performance status of no more than 2; (4) Satisfactory haematological parameters and heart, pulmonary, hepatic and renal functions; and (5) No sign of systemic infection, grade 3–4 bone marrow suppression, or severe coagulation dysfunction that cannot be corrected or contrast allergy.

Treatment Modalities

Patients with GCLM were treated according to the following instructions. First, the left-subclavian artery was

Table 1 Clinical Characteristics and Outcomes

Patient No.	Gender	Age	ECOG	Primary Tumor Resection	Onset of Liver Metastases	Extrahepatic Metastases	HAI OXA Cycles	2nd Cycle Response Evaluation	4th Cycle Response Evaluation	Adverse Events
1	M	58	I	N	Syn	Gastric, retroperitoneal lymph node	3.5	PR	PR	Drug allergy
2	M	66	I	N	Syn	Gastric, retroperitoneal lymph node	6	PR	SD	Grade 2 leukocytopenia
3	M	64	I	N	Syn	Gastric, abdominal lymph node	4	PR	PD	–
4	M	65	I	Y	Meta	Intersplenic lymph node	2	PR	PR	Grade 2 thrombocytopenia; mild anemia
5	M	53	I	Y	Meta	Retroperitoneal lymph node	6	PR	SD	Grade I liver damage

Abbreviations: Syn, synchronous; Meta, metachronous.

punctured by Seldinger method after ultrasonic localization, and then the catheter tip soaked with 1% heparin was placed at the opening of the celiac artery for selective celiac arteriography. Second, the catheter was replaced with a drug delivery device and the tip was placed in the common hepatic artery after the confirmation of the imaging. In particular, the catheter shape and head position of the drug delivery device were observed to be correct under fluoroscopy to ensure that the catheter was unobstructed and there was no leakage at the junction. Third, 10 mL 1% heparin fluid should be injected through the device before and after drug delivery. HAI oxaliplatin (70–80 mg/m² 2 hrs d1,15) was administered via the port-catheter system, combined with oral S-1 (50 mg twice daily for d1-14, 28 days for one cycle) as a first-line setting. The anticoagulation modality about heparin flushing should be executed at least once a month. Subsequently, HAI chemotherapy was ceased, and another treatment option was sought until one of the following events had occurred: progressive disease, catheter dysfunction and/or complications that prevented continual cure, or severe toxicity. The patients received further treatment thereafter according to the physician's prescription.

Evaluating Indicators

To fully evaluate the impact of HAI chemotherapy in these cases, pretreatment evaluation and follow-up examination were performed, including physical findings and laboratory tests (routine of blood, urine and stool, liver and renal functions, tumour marker). Chest and abdomen contrast-enhanced CT examinations were carried out at baseline within 1 week before treatment and then every 2–3 months thereafter. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours version 1.1:²⁰ complete response (CR), disappearance of all target lesions for at least 4 weeks; partial response (PR), at least a 30% decrease in the sum of the diameter of target lesions (including the longest diameter of the non-nodular lesion or the shortest diameter of the nodular lesion) for at least 4 weeks; stable disease (SD), neither sufficient decrease for partial response nor sufficient increase for progressive disease; or progressive disease (PD), at least a 20% increase in the total diameter of the target lesions and/or appearance of any new lesions. Adverse events, including haematologic, gastrointestinal, hepatorenal function and general disorders, were assessed based on the Common Terminology Criteria for Adverse Events version 4.0.

Results

The clinical characteristics and outcomes of the case series are detailed in Table 1. There were five males, and the median age was 61 years (range: 53–66 years). Three of these patients were newly diagnosed as GCLM, while the other patients developed multiple liver metastases a few months after radical gastrectomy for cancer. Moreover, except for liver metastases, all patients had extrahepatic lesions, mostly abdominal lymph node metastases, which showed bulky tumour burden and poor prognosis. Thus, HAI oxaliplatin plus oral S-1 was used to control both hepatic and extrahepatic metastases as a first-line setting. All patients underwent at least two cycles of HAI chemotherapy and successfully achieved a curative effect consequently. As shown in Figures 1 and 2, contrast-enhanced computed tomography (CT) images obtained before and after HAI chemotherapy showed obvious response in unresectable liver metastases at the end of 2nd cycle, accompanied by rapidly decreasing carcinoembryonic antigen (CEA) or carbohydrate antigen 19–9 (CA19-9) levels, indicating the achievement of a partial or even complete local response. Simultaneously, the clinical observation during treatment indicated that multiple liver metastases and discomfort in the upper abdomen were obviously reduced, and the basal levels of elevated alanine transaminase (ALT) or aspartate transaminase (AST) in patients No.1 and No.2 also decreased 3–5 times after combined therapy.

Until the 4th cycle response evaluation, the local effective rate [(PR+CR) %] and control rate [(CR+PR+SD) %] was 40% and 80%, respectively, only patient No.3 developed progression, and this patient would receive a randomized clinical trial in further treatment. To evaluate whether HAI chemotherapy has a liver-specific effect, progression-free survival was estimated separately from hepatic and extrahepatic metastases. As expected, HAI chemotherapy had a better local control against liver metastases (median PFS: hepatic, 8.8 months vs extrahepatic, 6.2 months; Figure 3). As shown in Table 1, patient No.1 would not receive a second-line therapy which combined HAI Irinotecan with oral Apatinib until the disease progressed (extrahepatic metastases). However, second-line therapy lasted for 5 months when hepatic progression appeared gradually. Patient No.2 replaced S-1 with Capecitabine when was found hepatic progression, who had a relatively longer PFS of 14 months. Among post-operative GCLM patients (No.4, 5 in Table 1) after failure of first-line combined therapy, they began second-line

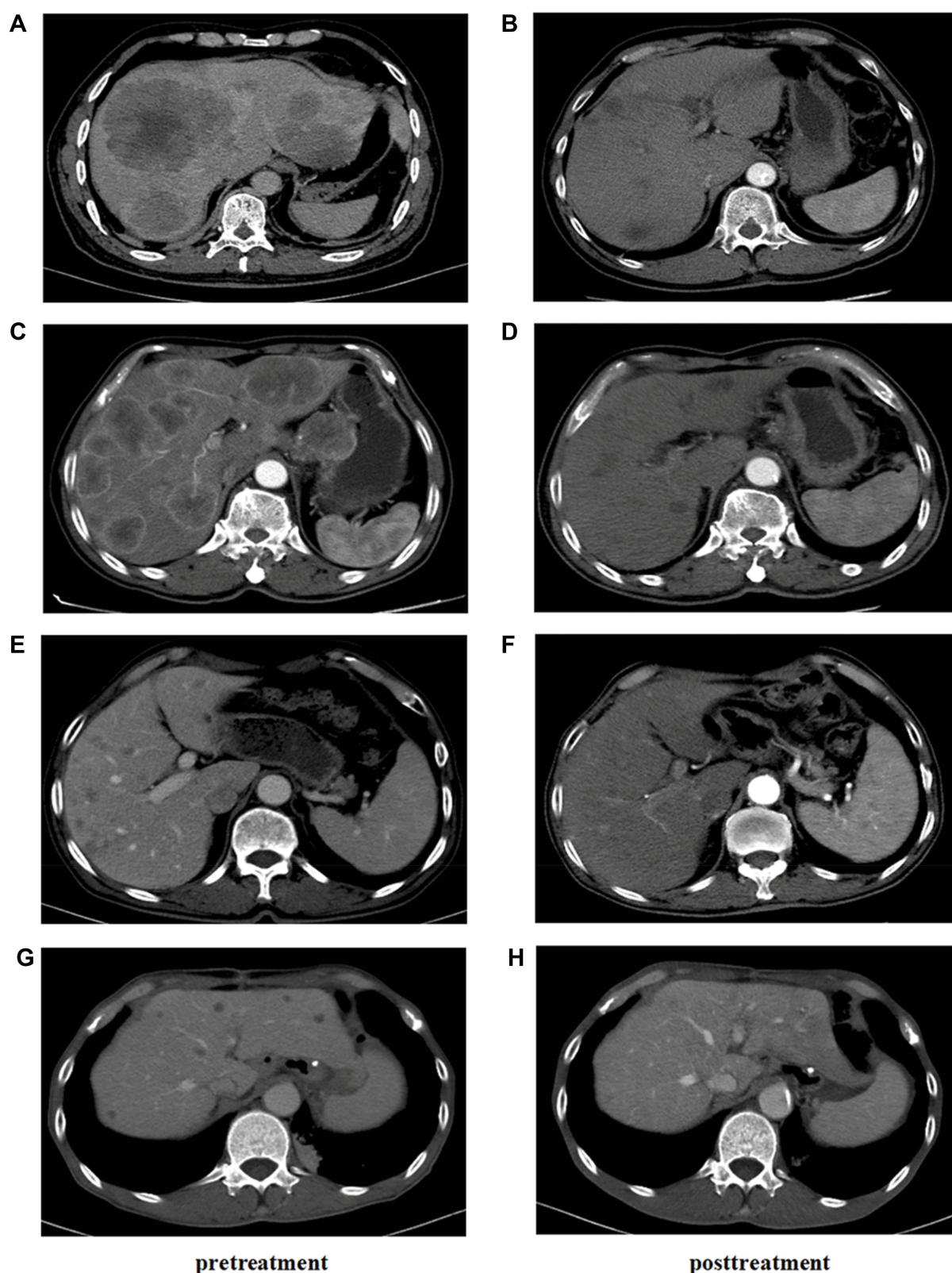


Figure 1 Follow-up CT scans after two cycles of HAI and systemic chemotherapy for each patient except No. 3 whose data were unavailable. (**A, B**) Patient No. 1, 58-year-old male showing marked liver metastases in CT images before therapy (**A**) and a significant shrinkage of the lesion after therapy (**B**). (**C, D**) Patient No. 2, 66-year-old male with unresectable liver metastases from gastric cancer (**C**) showing a decrease in the size and number of metastases after combined therapy (**D**). (**E, F**) Patient No. 4, 65-year-old male with multiple liver metastases after the failure of adjuvant therapy (**E**), showing the obvious response of lesions at 2 months after therapy (**F**). (**G, H**) Patient No. 5, 53-year-old male with multiple liver metastases after primary tumour resection (**G**) with a high-response rate in HAI, whose liver metastases disappeared gradually during treatment (**H**).

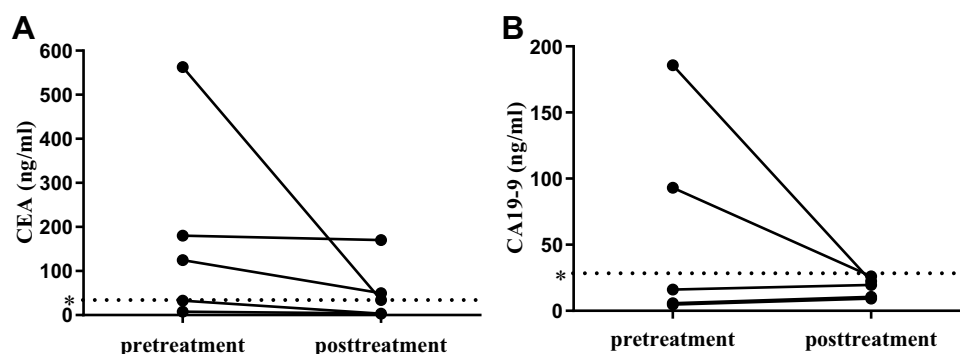


Figure 2 Changes in CEA (A) and CA19-9 (B) levels before and after two cycles of HAI and systemic chemotherapy. *upper limit of normal.

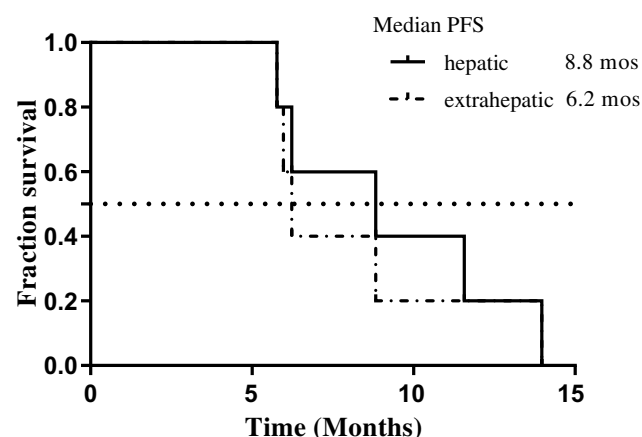


Figure 3 Kaplan–Meier hepatic and extrahepatic progression-free survival estimates for HAI oxaliplatin plus oral S-1 chemotherapy.

therapy: one with intravenous Taxane plus oral Apatinib, the other one with concurrent radiochemotherapy (retroperitoneal lymph node radiotherapy plus intravenous Taxane) combined with programmed cell death protein 1 (PD-1) checkpoint blockade, whose PFS was 5.8 months and 8.8 months, respectively.

To provide an overall assessment of HAI chemotherapy, the treatment feasibility and tolerance of HAI chemotherapy were observed during treatment. HAI oxaliplatin toxicities were recorded during course, which showed that there were no grade 3 or 4 adverse events affecting haematological, gastrointestinal, and hepatorenal functions, and the general condition of the patients was mild. Haematologic toxicity, including grade 2 leukocytopenia, thrombocytopenia and mild anaemia, was observed in patients No.2 and No.4. Grade 1 liver damage occurred in patient No.5, whose liver enzymes were slightly elevated. Notably, patient No.1 showed palpitation and chest distress when proceeding with HAI at the 4th cycle of chemotherapy due to an oxaliplatin allergy rather than progressive disease.

Discussion

GCLM presents a marked clinical challenge and always yields poor outcomes because most liver metastases are unresectable and often accompanied by extrahepatic lesions.^{21,22} In addition, the administration of conventional anticancer agents, such as systemic chemotherapy, is not sufficient to improve the efficacy against liver metastases, even when the primary tumour is resected.^{9–13} Surprisingly, there has been increasing consensus among experts that HAI chemotherapy could be a safe and high response local therapy.^{15,18,19,23,24} The rationale for HAI is the dual blood supply in the liver, namely, liver metastases derive a blood supply from the hepatic artery, while normal hepatocytes are supported by the portal vein.²⁵ HAI increases the concentration of drugs in local lesions and prolongs the time of drug action, which leads to the death of tumour cells directly and the inhibition of tumor proliferation.^{26–28} In terms of the technical aspects of arterial infusion we introduced here, HAI chemotherapy is often administered by surgically placing port-catheter system via the left subclavian or femoral access, while the former is preferred in our institution, above all because the left-subclavian artery way is cleaner and more easily for catheter care, which is also a minimally invasive safe access to intervene.^{29,30} In contrast to other types of local therapies for unresectable liver metastases, such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablative therapy (RFA), HAI provides the following benefits: (1) There are no significant differences between TACE and HAI in the overall response and recurrence rates, but TACE leads to more serious liver dysfunction compared to HAI, which will affect treatment compliance and the quality of life;³¹ (2) HAI is effective in both detectable liver lesions and intrahepatic micrometastases, whereas the therapeutic efficacy of RFA was reduced for large tumours, and the presence of as many as four or five lesions was considered suitable.^{18,32–34}

Based on previous clinical trials, combination chemotherapy with fluorouracil and platinum agents was recognized as a standard regimen for advanced metastatic gastric cancer.^{35,36} However, there is no established regimen or indication of HAI chemotherapy currently.³⁷ As far as HAI oxaliplatin is concerned, the oxaliplatin pharmacokinetic profile administered by HAI has a shorter terminal half-life³⁸ and a higher liver extraction rate of 0.47 than intravenous administration,^{39,40} which is the reason for the very favorable safety profile of this old drug in a new and innovative approach. Kumada et al¹⁵ launched a Phase II study that the overall response rate of combined administration of 5-fluorouracil, epirubicin and mitomycin-C by HAI in GCLM was 55.6%, the median overall survival was 10.5 months and the major prognosis-determining factor was the existence of extrahepatic lesions. However, in another study,¹⁸ HAI chemotherapy was employed in a second-line setting for patients with GCLM after the failure of systemic S-1 plus cisplatin. As a result, no survival benefit was observed during HAI chemotherapy. The controversial results were attributed to patient selection and combined therapy, assuming that survival benefit may be obtained from liver-only metastasis disease. Thus, for the existence of extrahepatic lesions, HAI chemotherapy should be combined with other systemic treatments to improve the overall response rate. While the efficacy of HAI chemotherapy plus systemic treatment for liver metastases from colorectal cancer has been confirmed,^{41,42} the significance of this combined therapy for GCLM is still unclear.

In our opinion, HAI oxaliplatin plus oral S-1 chemotherapy can be considered as a new choice of first-line treatment for GCLM, which is also a good approach for controlling extrahepatic lesions with less adverse events. By reporting these cases, we would like to emphasize that this combined therapy is usually conservative, palliative and aimed at reducing the patient's discomfort, improving the quality of life and prolonging survival time. However, there were several limitations to our study. First, this study was based on a retrospective analysis of a small sample size from a single institution, and we could not cover all adverse events due to the small number of cases. Certainly, it is necessary to perform subgroup analysis stratified by the timing of liver metastases status in the assessment of efficacy and risk. Second, our analysis did not find a correlation of response to HAI chemotherapy with overall survival time for the endpoint of follow-up. Third, the present protocol did not routinely use HAI

oxaliplatin and oral S-1 chemotherapy in combination, suggesting that the assessment of the curative effect must be further objectified and standardized by a prospective multicentre clinical trial. To achieve improved outcomes, patients need to be selected carefully, and close monitoring is required for adverse events because the addition of concomitant systemic chemotherapy can increase the toxicity of HAI pump therapy.⁴³ We are presumed that this study could be a step to seek an optimal treatment strategy for GCLM.

Abbreviations

HAI, Hepatic arterial infusion; GCLM, Gastric cancer with multiple liver metastases; CEA, Carcinoembryonic antigen; CA19-9, Carbohydrate antigen; PR, Partial response; CR, Complete response; SD, Stable disease; PD, Progressive disease; FEM, fluorouracil, epirubicin, mitomycin C; ECOG, the Eastern Cooperative Oncology Group; ALT, Alanine transaminase; AST, Aspartate transaminase; PFS, progression-free survival; TACE, Transcatheter arterial chemoembolization; RFA, Radiofrequency ablative therapy; RCT, Randomized clinical trial; OXA, Oxaliplatin; Syn, Synchronous; Meta, Metachronous; CT, computed tomography; PD-1, programmed cell death protein 1.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate for all the patients were obtained before therapy.

Acknowledgments

This study was supported by the National Key Research and Development Program of China (No. 2017YFC1308900); Scientific and Technological Development Program of Nanjing (No. YKK18078); and the National Natural Science Foundation of China (Grant No. 81803093).

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. 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. doi:10.3322/caac.21492
2. Shin A, Kim J, Park S. Gastric cancer epidemiology in Korea. *J Gastric Cancer*. 2011;11(3):135–140. doi:10.5230/jgc.2011.11.3.135

3. Schlansky B, Sonnenberg A. Epidemiology of noncardia gastric adenocarcinoma in the United States. *Am J Gastroenterol*. 2011;106(11):1978–1985. doi:10.1038/ajg.2011.213
4. Douglass HO Jr, Hundahl SA, Macdonald JS, Khatri VP. Gastric cancer: D2 dissection or low maruyama Index-based surgery—a debate. *Surg Oncol Clin N Am*. 2007;16(1):133–155. doi:10.1016/j.soc.2006.10.005
5. Fujisaki S, Tomita R, Nezu T, Kimizuka K, Park E, Fukuzawa M. Prognostic studies on gastric cancer with concomitant liver metastases. *Hepato-Gastroenterology*. 2001;48(39):892–894.
6. Koga S, Kawaguchi H, Kishimoto H, et al. Therapeutic significance of noncurative gastrectomy for gastric cancer with liver metastasis. *Am J Surg*. 1980;140(3):356–359. doi:10.1016/0002-9610(80)90167-1
7. Okuyama K, Isono K, Juan IK, et al. Evaluation of treatment for gastric cancer with liver metastasis. *Cancer*. 1985;55(10):2498–2505. doi:10.1002/1097-0142(19850515)55:10<2498::AID-CNCR2820551032>3.0.CO;2-S
8. Ueda K, Iwahashi M, Nakamori M, et al. Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer. *Langenbecks Arch Surg*. 2009;394(4):647–653. doi:10.1007/s00423-008-0311-9
9. Jerraya H, Saidani A, Khalfallah M, Bouasker I, Nouri R, Dziri C. Management of liver metastases from gastric carcinoma: where is the evidence? *Tunis Med*. 2013;91(1):1–5.
10. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a Phase 3, open-label, randomised controlled trial. *Lancet (London, England)*. 2010;376(9742):687–697. doi:10.1016/S0140-6736(10)61121-X
11. Koizumi W, Kim YH, Fujii M, et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). *J Cancer Res Clin Oncol*. 2014;140(2):319–328. doi:10.1007/s00432-013-1563-5
12. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a Phase III trial. *Lancet Oncol*. 2008;9(3):215–221. doi:10.1016/S1470-2045(08)70035-4
13. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer*. 2011;14(1):72–80. doi:10.1007/s10120-011-0009-5
14. 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):1395–1403. doi:10.1200/JCO.2005.03.8166
15. Kumada T, Arai Y, Itoh K, et al. Phase II study of combined administration of 5-fluorouracil, epirubicin and mitomycin-C by hepatic artery infusion in patients with liver metastases of gastric cancer. *Oncology*. 1999;57(3):216–223. doi:10.1159/000012034
16. Melichar B, Voboril Z, Cerman J Jr, et al. Hepatic arterial infusion chemotherapy in gastric cancer: a report of four cases and analysis of the literature. *Tumori*. 2004;90(4):428–434. doi:10.1177/030089160409000414
17. Ojima H, Ootake S, Yokobori T, et al. Treatment of multiple liver metastasis from gastric carcinoma. *World J Surg Oncol*. 2007;5:70. doi:10.1186/1477-7819-5-70
18. Seki H, Ohi H, Ozaki T, Yabusaki H. Hepatic arterial infusion chemotherapy using fluorouracil, epirubicin, and mitomycin C for patients with liver metastases from gastric cancer after treatment failure of systemic S-1 plus cisplatin. *Acta Radiol*. 2016;57(7):781–788. doi:10.1177/0284185115603247
19. Fukami Y, Kaneoka Y, Maeda A, et al. Adjuvant hepatic artery infusion chemotherapy after hemihepatectomy for gastric cancer liver metastases. *Int J Surg*. 2017;46:79–84. doi:10.1016/j.ijsu.2017.08.578
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205–216. doi:10.1093/jnci/92.3.205
21. Kakeji Y, Morita M, Maehara Y. Strategies for treating liver metastasis from gastric cancer. *Surg Today*. 2010;40(4):287–294. doi:10.1007/s00595-009-4152-0
22. Sakamoto Y, Sano T, Shimada K, et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. *J Surg Oncol*. 2007;95(7):534–539. doi:10.1002/(ISSN)1096-9098
23. Arai Y, Endo T, Sone Y, et al. Management of patients with unresectable liver metastases from colorectal and gastric cancer employing an implantable port system. *Cancer Chemother Pharmacol*. 1992;31(Suppl):S99–S102. doi:10.1007/BF00687116
24. Yonemura Y, Matuki N, Sakuma H, et al. Effect of intra-hepatoarterial infusion of MMC and CDDP for gastric cancer patients with liver metastases. *Surg Today*. 1992;22(3):253–259. doi:10.1007/BF00308831
25. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol*. 1954;30(5):969–977.
26. Peng Z, Xu S, Li H, Sun C, Fu M, Gao M. Advanced gastric cancer with brain metastasis effectively treated by arterial infusion chemotherapy: a case report. *Oncol Lett*. 2014;7(2):449–451. doi:10.3892/ol.2013.1699
27. Polysalov VN, Veriasova NN, Dolgikh SD, Gapbarov A. Regional chemotherapy in locally advanced and metastatic gastric cancer. *Vopr Onkol*. 2012;58(6):762–767.
28. Ning Z, Chen D, Liu A, et al. Efficacy of chemotherapy combined with targeted arterial infusion of verapamil in patients with advanced gastric cancer. *Cell Biochem Biophys*. 2014;68(1):195–200. doi:10.1007/s12013-013-9689-2
29. Hildebrandt B, Pech M, Nicolaou A, et al. Interventionally implanted port catheter systems for hepatic arterial infusion of chemotherapy in patients with colorectal liver metastases: a Phase II-study and historical comparison with the surgical approach. *BMC Cancer*. 2007;7:69. doi:10.1186/1471-2407-7-69
30. Imamine R, Shibata T, Shinozuka K, Togashi K. Complications in hepatic arterial infusion chemotherapy: retrospective comparison of catheter tip placement in the right/left hepatic artery vs. the gastroduodenal artery. *Surg Today*. 2017;47(7):851–858. doi:10.1007/s00595-016-1465-7
31. Chen J, Zhang Y, Cai H, Yang Y, Fei Duan Y. Comparison of the effects of postoperative prophylactic transcatheter arterial chemoembolization (TACE) and transhepatic arterial infusion (TAI) after hepatectomy for primary liver cancer. *J BUON*. 2018;23(3):629–634.
32. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the “test-of-time approach”. *Cancer*. 2003;97(12):3027–3035. doi:10.1002/(ISSN)1097-0142
33. de Baere T, Elias D, Dromain C, et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. *AJR Am J Roentgenol*. 2000;175(6):1619–1625. doi:10.2214/ajr.175.6.1751619
34. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology*. 2001;221(1):159–166. doi:10.1148/radiol.2211001624
35. Cunningham D, Okines AF, Ashley S. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med*. 2010;362(9):858–859. doi:10.1056/NEJMc0911925
36. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol*. 2010;28(9):1547–1553. doi:10.1200/JCO.2009.25.4706

37. Zervoudakis A, Boucher T, Kemeny NE. Treatment options in colorectal liver metastases: hepatic arterial infusion. *Visc Med.* **2017**;33(1):47–53. doi:10.1159/000454693
38. Kern W, Beckert B, Lang N, et al. Phase I and pharmacokinetic study of hepatic arterial infusion with oxaliplatin in combination with folinic acid and 5-fluorouracil in patients with hepatic metastases from colorectal cancer. *Ann Oncol.* **2001**;12(5):599–603. doi:10.1023/A:1011186708754
39. 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):5203–5208.
40. 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):141. doi:10.3390/cancers11020141
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):3465–3471. doi:10.1200/JCO.2008.20.1301
42. Kemeny N, Gonen M, Sullivan D, et al. Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. *J Clin Oncol.* **2001**;19(10):2687–2695. doi:10.1200/JCO.2001.19.10.2687
43. 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):1236–1241. doi:10.1093/annonc/mdn769

Cancer Management and Research

Dovepress

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>