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ORIGINAL RESEARCH

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

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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/m^2 2 hrs d1,15) administered via a port-catheter system and S-1 with oral (35–40 mg/m^2 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 al[18] 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 al[19] 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	1	N	Syn	Gastric, retroperitoneal lymph node	3.5	PR	PR	Drug allergy
2	M	66	1	N	Syn	Gastric, retroperitoneal lymph node	6	PR	SD	Grade 2 leukocytopenia
3	M	64	1	N	Syn	Gastric, abdominal lymph node	4	PR	PD	–
4	M	65	1	Y	Meta	Intersplenic lymph node	2	PR	PR	Grade 2 thrombocytopenia; mild anemia
5	M	53	1	Y	Meta	Retroperitoneal lymph node	6	PR	SD	Grade 1 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/m^2 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

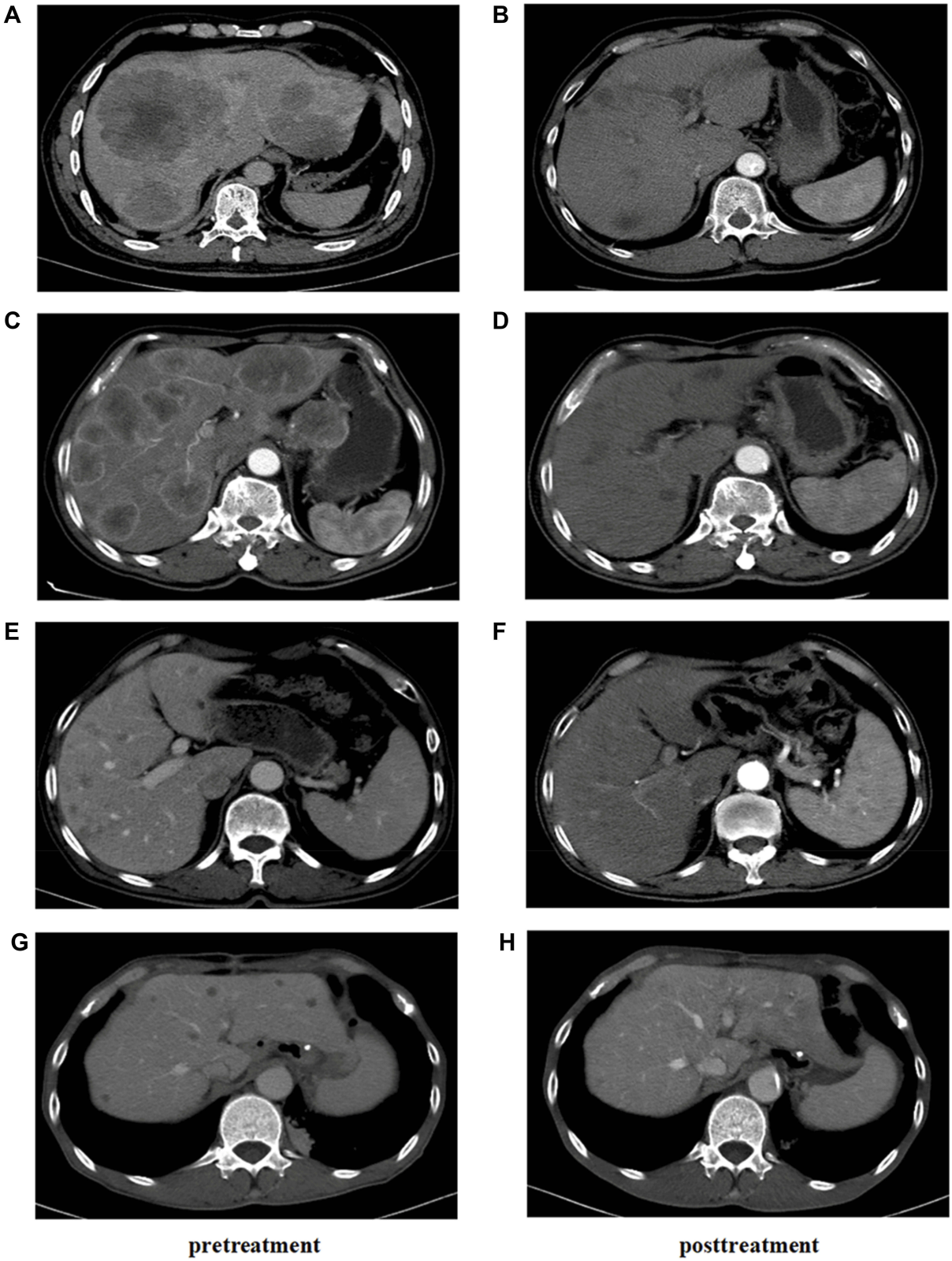

Figure 1 Follow-up CT scans after two cycles of HAI and systemic chemotherapy for each patient except No. 3 whose data were unavailable. (**A, B**) Patient No.1, 58-year-old male showing marked liver metastases in CT images before therapy (**A**) and a significant shrinkage of the lesion after therapy (**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**).

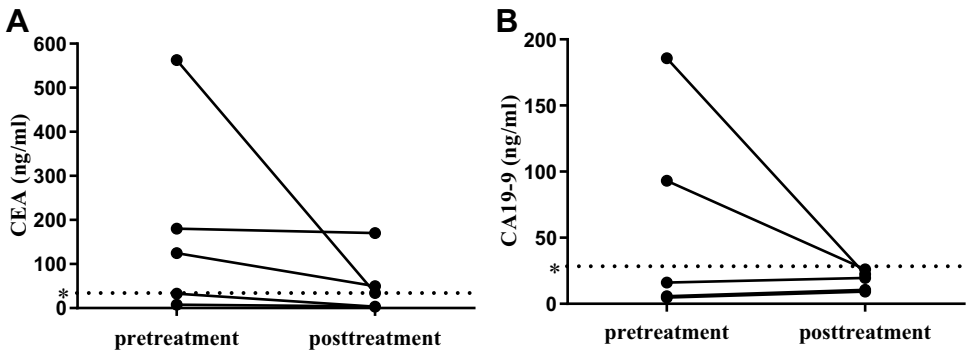

Figure 2 Changes in CEA (**A**) and CA19-9 (**B**) levels before and after two cycles of HAI and systemic chemotherapy. *upper limit of normal.

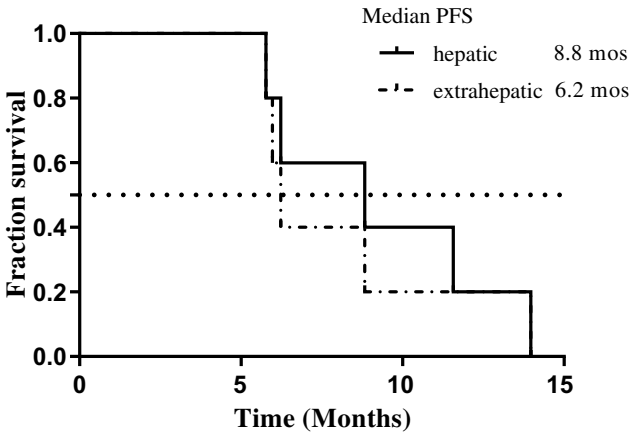

Figure 3 Kaplan–Meier hepatic and extrahepatic progression-free survival estimates for HAI oxaliplatin plus oral S-1 chemotherapy.

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-life[38] 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 al[15] 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.

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Disclosure

The authors declare that they have no conflicts of interest.

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