Original Article

Hepatic arterial infusion chemotherapy combined with bevacizumab plus a PD-1 inhibitor for gallbladder cancer with hepatic oligometastasis: a real-world study

Wenchao Zhao[1#], Zhiyuan Yao[1,2#], Jingbo Li[1#], Wenping Li[3], Qi Dou[4], Xiangfei Zhao[5], Yintao Wu[1], Nianxin Xia[1]

[1]Faculty of Hepato-Pancreato-Biliary Surgery, Chinese PLA General Hospital, Beijing, China; [2]Medical School of Chinese PLA, Beijing, China; [3]Department of Medical Imaging, the Sixth Medical Center of Chinese PLA General Hospital, Beijing, China; [4]Department of Nuclear Medicine, the Sixth Medical Center of Chinese PLA General Hospital, Beijing, China; [5]Department of Oncology, Chinese PLA General Hospital, Beijing, China

Contributions: (I) Conception and design: N Xia; (II) Administrative support: N Xia; (III) Provision of study materials or patients: N Xia, W Zhao, Y Wu; (IV) Collection and assembly of data: W Zhao, Z Yao, J Li; (V) Data analysis and interpretation: W Zhao, Z Yao, J Li, Q Dou, W Li, X Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Dr. Nianxin Xia, MD. Faculty of Hepato-Pancreato-Biliary Surgery, Chinese PLA General Hospital, 6 Fucheng Road, Beijing 100048, China. Email: doctorxnx@163.com.

Background: Gallbladder cancer (GBC) is different from other biliary tract cancers in terms of molecular phenotype and microenvironment. Specific treatments for GBC need to be urgently explored. This study preliminarily investigated the clinical value of hepatic artery infusion chemotherapy (HAIC) combined with bevacizumab plus a programmed death receptor-1 (PD-1) inhibitor for treatment of GBC with hepatic oligometastasis.

Methods: We retrospectively collected data on GBC patients with hepatic oligometastasis, who received this combination therapy. The clinical data, conversion rate, treatment response, adverse events (AEs), and short-term survival were summarized. The responses of primary gallbladder lesions and hepatic metastasis, and their effect on prognosis, were investigated.

Results: A total of 27 patients were included in the analysis. No grade 4 AEs were observed. The overall objective response rate (ORR) was 55.6% and the disease control rate (DCR) was 85.2%. Median overall survival (OS) time was 15.0 months and the 1-year survival rate was 64.0%. Median progression-free survival (PFS) time was 7.0 months and the 1-year PFS rate was 16.2%. Six patients (22.2%) were successfully converted to resection. Compared with primary gallbladder lesions, it appeared more difficult for patients with hepatic metastasis to achieve remission (ORR: 40.7% *vs.* 77.8%; P=0.012), but its response appeared to be closely related to the prognosis [median OS: 16.0 months in the complete response (CR) or partial response (PR) group *vs.* 11.0 months in the stable disease (SD) or progressive disease (PD) group, P=0.070; median PFS: 12.0 months in the CR or PR group *vs.* 6.5 months in the SD or PD group, P<0.001]. Preoperative CA19-9 of >1,900 U/mL and >5 cm metastatic lesions were associated with an unsatisfactory response, whereas a significant decrease of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake may be a marker of tumor remission.

Conclusions: The combination of HAIC, a PD-1 inhibitor, and bevacizumab shows potential for advanced GBC with hepatic oligometastasis. The therapeutic response of hepatic metastasis had a greater influence on prognosis than that of primary gallbladder lesions.

Keywords: Gallbladder cancer (GBC); programmed death receptor-1 inhibitor (PD-1 inhibitor); bevacizumab; hepatic arterial infusion chemotherapy

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Introduction

Gallbladder cancer (GBC) accounts for 80–95% of all biliary tract cancers (BTCs) (1). The prognosis for GBC is extremely poor with median overall survival (OS) of 4–7 months (2). Radical resection is the first option and only curative treatment for GBC. In patients who receive a curative resection, 5-year OS rates range from 15% to 20% (3). Unfortunately, most GBC cases are diagnosed at an advanced or terminal stage and are contraindicated for surgery (4). Patients with unresectable GBC have a dismal prognosis with 5-year OS rates of <5% (5).

The current first-line choice of chemotherapy for advanced BTC is gemcitabine plus cisplatin (GC). Recently, two randomized, double-blind phase III trials demonstrated that GC plus immunotherapy shows promising efficacy and acceptable safety in patients with advanced BTC with median OS of 12.7–12.8 months (6,7). In accordance with the National Comprehensive Cancer Network (NCCN) guideline, GC plus durvalumab, a programmed cell death ligand 1 (PD-L1) inhibitor, is considered to be the preferred regimen for unresectable BTC (8). Several new strategies have been evaluated for BTC treatment. Targeted-immune therapy offers another option and exerts a synergistic effect with chemotherapy. A programmed death receptor-1 (PD-1) inhibitor plus lenvatinib for advanced GBC achieved an objective response rate (ORR) of 32.3% (9). Hepatic artery infusion chemotherapy (HAIC) has achieved encouraging response rates in hepatocellular carcinoma (HCC) and colorectal liver metastasis (10,11). HAIC has been recently proven to be effective for patients with intrahepatic and perihilar cholangiocarcinoma (12,13). In patients with GBC, HAIC with oxaliplatin and 5-fluorouracil achieved an ORR of 69.2% (14). Based on results above, for well-tolerated patients, the combination of multiple treatment modalities is reasonable and beneficial.

GBC is quite different from other BTCs in terms of molecular phenotype, microenvironment, and survival outcome. The data of GBC in clinical trials are often included in the basket of BTC. Specific treatments for GBC should be urgently explored. GBC frequently spreads to the liver (15). The term oligometastasis indicates that tumors progress to a limited number of metastatic lesions with the potential to benefit from local therapies, such as ablation, resection, and stereotactic radiotherapy (16). Cases of hepatic oligometastasis without hilar invasion and distant lymphatic metastasis account for a small proportion of GBC patients. However, these patients usually have adequate liver functions and limited tumor involvement, and have the potential to be converted to resection. Long-term survival has been reported in this group of patients (17,18). Therefore, GBC patients with hepatic oligometastasis may benefit from multidisciplinary treatments (MDTs).

Owing to the promising results, we preliminary explored the safety and effect of HAIC (oxaliplatin, 5-fluorouracil, and leucovorin, FOLFOX) combined with bevacizumab plus a PD-1 inhibitor for GBC with hepatic oligometastasis. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-816/rc).

Highlight box

Key findings

- The combination of hepatic artery infusion chemotherapy (HAIC), programmed death receptor-1 (PD-1) inhibitor and bevacizumab showed its potential value for advanced gallbladder cancer (GBC) with hepatic oligometastasis.

What is known and what is new?

- The current first-line choice for advanced GBC is gemcitabine plus cisplatin combined with durvalumab.
- The strategy of HAIC (oxaliplatin, 5-fluorouracil, leucovorin) combined with bevacizumab plus PD-1 inhibitor has promising prospect in treating GBC with hepatic oligometastasis. The safety and tolerance were acceptable.

What is the implication, and what should change now?

- Locoregional chemotherapy combined with immune-targeted therapy should be considered reasonably for selected patients with advanced GBC.

Methods

Study population

From January 2020 to December 2022, all GBC patients who received treatment at the Branch Ward of the Faculty of Hepato-Pancreato-Biliary Surgery, Chinese People's Liberation Army (PLA) General Hospital were reviewed. The inclusion criteria were as follows: diagnosed as GBC by pathological examination; hepatic metastasis, defined as a discrete hepatic lesion separate from the primary tumor, measured by computed tomography (CT) or magnetic resonance imaging (MRI); radiographically detectable lymph node metastasis was confined to the hilar of liver (lymph metastasis was considered if any of the following criteria were met: short-axis diameter larger than 10 mm,

abnormal round morphology, non-uniform density, non-uniform enhancement, internal necrosis, lymph node fusion, ill-defined borders, or involvement of surrounding organs or blood vessels) (19); received HAIC + bevacizumab + a PD-1 inhibitor as first therapy; and adequate liver function (Child-Pugh A) and other vital organ functions before treatment. The exclusion criteria were as follows: GBC with obstructive jaundice; GBC with invasion of the hepatic artery or portal vein in the hilar region; and previous other forms of treatment, such as resection, systematic chemotherapy, or radiotherapy. This retrospective study was approved by the Ethics Committee of the Sixth Medical Center of Chinese PLA General Hospital (No. HZKY-PJ-2023-44). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All treatment decisions were made at the patient's discretion with informed consent. Patient privacy was fully protected.

Pretreatment assessment

Abdominal ultrasonography, enhanced CT, or MRI was used to assess the size and location of GBC and hepatic metastasis. Thoracic CT was performed to evaluate signs of lung metastasis. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) was used to detect distal metastasis. The maximum ^{18}F-FDG standard uptake value (SUV) in the delay phase was collected in this study. Tumor markers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), were routinely examined.

A complete blood count was obtained for each patient. Liver function was evaluated by measuring serum total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin, albumin (ALB), prealbumin, alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) levels. Prothrombin time (PT) was measured to evaluate liver function and surgical safety. Routine pulmonary function tests and cardiovascular Doppler ultrasound were performed to evaluate signs of any contraindications to resection.

Treatment

Bevacizumab [Avastin, Roche Pharma (Switzerland) Ltd.] was administered at 7.5 mg/kg every 3 weeks until tumor progression or the occurrence of intolerant adverse events (AEs). Sintilimab, a PD-1 inhibitor (Innovent Biologics Suzhou Co. Ltd., China), was administered at 200 mg every 3 weeks, starting on the same day of bevacizumab administration.

HAIC was performed within 3 days after sintilimab and bevacizumab were administrated. After femoral artery puncture and catheterization, arteriography of the coeliac artery (CA) and superior mesenteric artery (SMA) was performed to detect the tumor blood supply. Then, a microcatheter (Terumo Corp., Tokyo, Japan) was inserted into the proper hepatic artery. We did not embolize gastroduodenal artery (GDA) and right gastric artery (RGA) which are routinely performed at other centers (10,12,14) to make the chemotherapeutics cover the hilar region of the liver. A modified FOLFOX-6 regimen (oxaliplatin at 85 mg/m^2 from hour 0 to 2 on day 1; leucovorin at 400 mg/m^2 from hour 2 to 3 on day 1; 5-fluorouracil at 400 mg/m^2 bolus at hour 3 on day 1; 5-fluorouracil at 2,400 mg/m^2 over 46 hours on days 1–2) was then administrated.

Evaluation of the tumor response

The combination therapy was administered in a 3-week cycle. After every two cycles, the tumor response was evaluated by RECIST 1.1 (response evaluation criteria in solid tumor 1.1) by radiologists at the Department of Medical Imaging (20). The clinical outcomes were defined as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The ORR was calculated as the proportion of cases with a best overall response of CR or PR. The disease control rate (DCR) was calculated as the proportion of cases with a best overall response of CR, PR, or SD. If the following conditions were met, surgical resection was considered: tumors were significantly reduced in size without extrahepatic metastasis; no new lesions detected; and tumors were evaluated to be safe to resect. For patients with SD or PD, systematic therapy continued depending on the patient's tolerance. Once extrahepatic metastasis was observed, systematic chemotherapy was applied instead of HAIC. The maximum course of HAIC treatment did not exceed six cycles. All recommendations were made by a MDT conference, including specialists in oncology, surgery, radiology, and interventional therapy. The final decisions were made at the patient's discretion with informed consent. AEs were assessed by CTCAE (Common Terminology Criteria for Adverse Events, version 5.0).

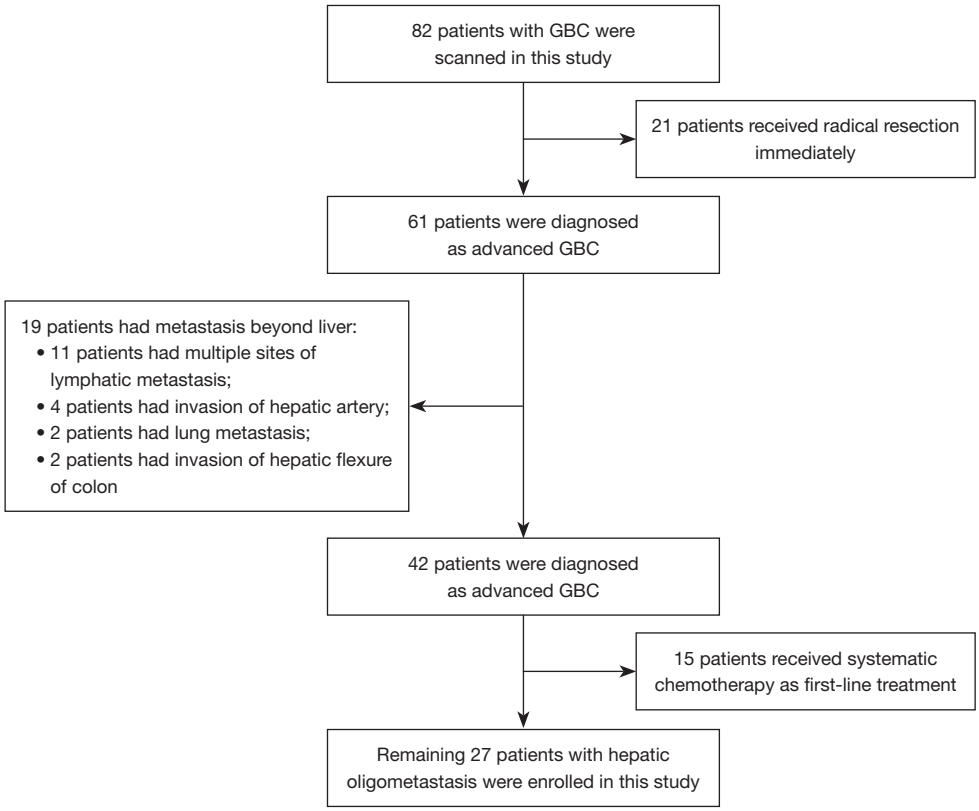

Figure 1 Flow diagram of study population enrolled in this study. GBC, gallbladder cancer.

Follow-up

All patients were closely followed up by outpatient visits or social network platforms because of the coronavirus pandemic. Laboratory examinations were performed every 2–4 weeks, and CT/MRI was performed regularly. ^{18}F-FDG PET-CT was performed every two to four cycles.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation and were compared using the unpaired *t*-test. When continuous variable data did not conform to a normal distribution, data are expressed as the median (range) and were compared using the Mann-Whitney *U*-test. Categorical data were compared by the χ^2 test with Fisher's exact test. Survival analyses were performed by the Kaplan-Meier method. OS was calculated from the initial day of combination treatment to the day of death or the most recent follow-up visit. Progression-free survival (PFS) was calculated from the initial day of combination treatment to the first follow-up visit at which clear evidence of tumor progression was observed or the most recent follow-up visit. A P value of less than 0.05 was considered significant. All statistical analyses were performed using IBM SPSS for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) and R program (Version 4.2.2).

Results

Baseline characteristics of enrolled patients

A total of 82 GBC patients who received treatment at our center were assessed. Fifty-five patients were excluded from the study population. Among them, 21 patients received an upfront radical resection, 19 patients had extrahepatic metastasis, and 15 patients received systematic chemotherapy. The remaining 27 patients who received HAIC combined with bevacizumab plus sintilimab were enrolled in this study (*Figure 1*). Their baseline characteristics are shown in *Table 1*.

Notably, 18 (66.7%) patients had CA19-9 >1,900 U/mL (the upper limit of the measurable value in our center). All patients had a primary lesion on the hepatic side of

Table 1 Baseline characteristics of the enrolled patients

Variables	Total (n=27)
Age (years)	66 [45–85]
Gender	
Female	15 (55.6)
Male	12 (44.4)
ECOG performance score	
0	25 (92.6)
1	2 (7.4)
CA19-9	
>1,900 U/mL	18 (66.7)
≤1,900 U/mL	9 (33.3)
Site of gallbladder cancer	
Peritoneal side	0
Hepatic side	18 (66.7)
Diffused	9 (33.3)
Number of liver metastasis	
1–3	21 (77.8)
4–5	3 (11.1)
>5	3 (11.1)
Detectable hilar lymph metastasis[†]	9 (33.3)
Extent of metastasis involvement	
Limited to hemiliver	17 (63.0)
Extended to hemiliver	10 (37.0)
Size of primary lesions (cm)	3.5 [1.9–5.2]
Largest size of metastasis (cm)	3.2 [1.0–10.1]
^{18}F-FDG standard uptake value[‡]	
Primary gallbladder lesions	5.3 [2.6–16.5]
Hepatic metastasis	4.5 [3.1–15.1]
Preoperative laboratory test	
WBC (×10^9/L)	6.91 [3.11–10.51]
HGB (g/L)	119 [86–144]
PLT (×10^9/L)	246 [135–357]
PT (s)	11.9 [11.0–13.8]
TBIL (μmol/L)	11.2 [6.8–40.1]
ALB (g/L)	35.9 [31.1–46.1]
ALT (U/mL)	30.8 [10.7–111.7]
GGT (U/mL)	99.8 [22.9–662.9]
Creatinine (mmol/L)	69.3 [49.8–98.1]

Data are presented as n (%) or median [range]. [†], CT-determined lymph metastasis, which was considered if any of the following criteria were met: short-axis diameter larger than 10 mm, abnormal round morphology, non-uniform density, non-uniform enhancement, internal necrosis, LN fusion, ill-defined borders, or involvement of surrounding organs or blood vessels (18); [‡], ^{18}F-FDG standard uptake value was the maximum value of lesions in delay phase. For hepatic metastasis, we adopt the value of target lesions. ECOG, eastern cooperative oncology group; CA19-9, carbohydrate antigen 19-9; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; WBC, white blood cells; HGB, hemoglobulin; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, gamma-glutamine transpeptidase; CT, computed tomography.

the gallbladder. Six (22.2%) patients had more than three lesions of hepatic metastasis. Ten (37.0%) patients had liver metastasis spreading over the hemiliver. Nine patients (33.3%) had radiographically detectable lymph metastasis at the hilar of liver. The median size of primary lesions was 3.5 cm (range, 1.9–5.2 cm). The median size of metastatic lesions was 3.2 cm (range, 1.0–10.1 cm).

Tumor response and short-term survival

For all patients enrolled in this study, the median time of follow-up was 11.0 months (range, 6–26 months). In brief, no patient achieved CR, 15 patients achieved PR, eight patients exhibited SD, and four patients exhibited PD. The overall ORR was 55.6% and DCR was 85.2%. For all patients, the median OS was 15.0 months [range, 11–not applicable (NA) months], and the 1-year survival rate was 64.0% (*Figure 2A*). Median PFS was 7.0 months (range, 7–11 months), and the 1-year PFS rate was 16.2% (*Figure 2B*).

We further compared the treatment response of primary gallbladder lesions and hepatic metastasis. For primary gallbladder lesions, one patient achieved CR, 20 patients achieved PR, and six patients exhibited SD. The ORR of primary lesions was 77.8%, and the DCR was 100%. For hepatic metastasis, no patient achieved CR, 11 patients achieved PR, 13 patients exhibited SD, and three patients exhibited PD (*Figure 3*). Compared with hepatic metastasis, primary lesions

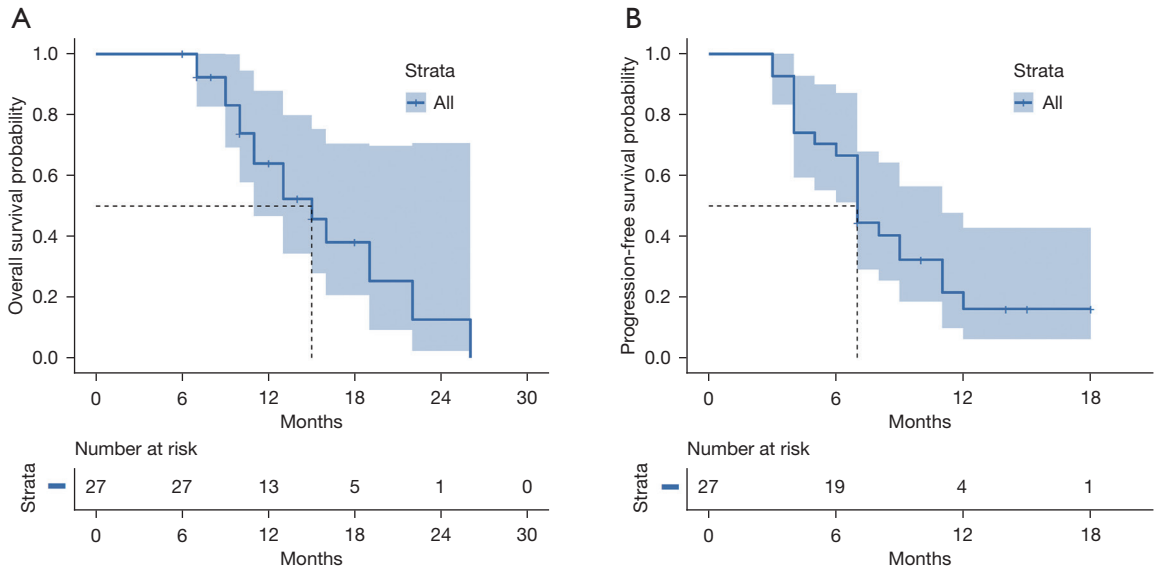

Figure 2 Kaplan-Meier survival curves of OS (A) and PFS time (B) of the entire cohort. The median OS was 15.0 months (range, 11–NA months) and the 1-year survival rate was 64.0%. The median PFS was 7.0 months (range, 7–11 months) and the 1-year PFS rate was 16.2%. OS, overall survival; PFS, progression-free survival; NA, not applicable.

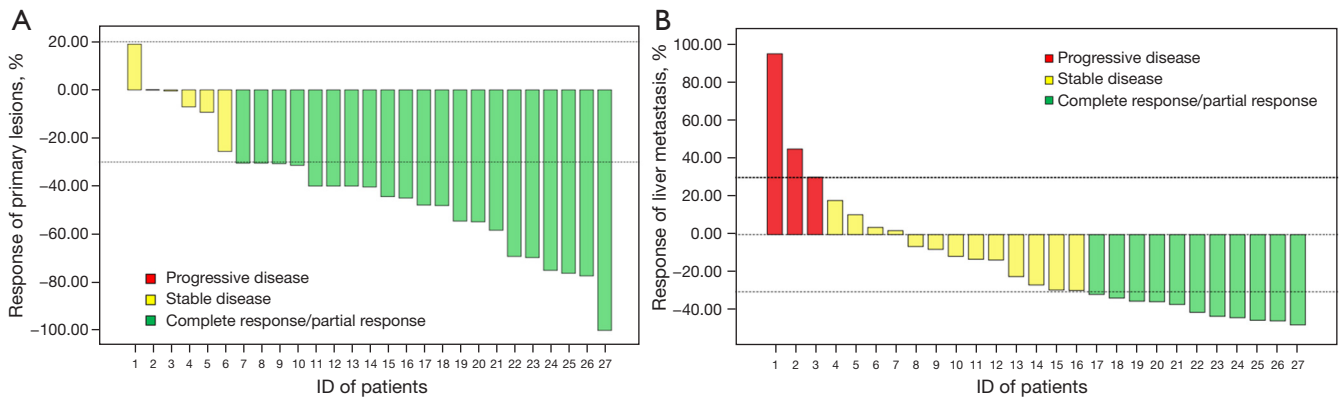

Figure 3 Waterfall plot for changes in size of target lesions. (A) Response of primary gallbladder lesions with an ORR of 77.8% and a DCR of 100%. (B) Response of hepatic metastasis with an ORR of 40.7% and a DCR of 88.9%. Primary gallbladder lesions had higher incidence of objective response compared with hepatic metastases (P=0.012). ORR, objective response rate; DCR, disease control rate.

were more likely to exhibit remission after combination therapy (*Table 2*, ORR: 77.8% *vs.* 40.7%, P=0.012).

We also compared the effect of response on prognosis between primary lesions and hepatic metastasis. When we focused on primary lesions, median OS was 15.0 months (range, 11–NA months) for patients who achieved a response (CR or PR) compared with 15.0 months (range, 9–NA months) for patients who exhibited a non-response (SD or PD) (P=0.809, *Figure 4A*). Median PFS was 7 months (range, 4–NA months) for patients who achieved a response and 7 months (range, 7–NA months) for patients who exhibited a non-response (P=0.447, *Figure 4B*). When we focused on hepatic metastasis, median OS was 16 months (range, 15–NA months) for patients who achieved a response compared with 11 months (range, 10–NA months) for patients who exhibited a non-response (P=0.070, *Figure 5A*). Median PFS was 12 months (range, 8–NA months) for patients who achieved a response compared with 6.5 months (range, 4–9 months) for who patients exhibited a non-response (P<0.001, *Figure 5B*).

Table 2 Tumor response after combination treatment according to RECIST 1.1

Tumor response	Overall response	Response		
		Primary lesions	Hepatic metastasis	P value
Complete response	0	1	0	0.027
Partial response	15	20	11	–
Stable disease	8	6	13	–
Progressive diseases	4	0	3	–
Objective response rate	55.6%	77.8%	40.7%	0.012
Disease control rate	85.2%	100%	88.9%	0.236

RECIST 1.1, response evaluation criteria in solid tumor 1.1.

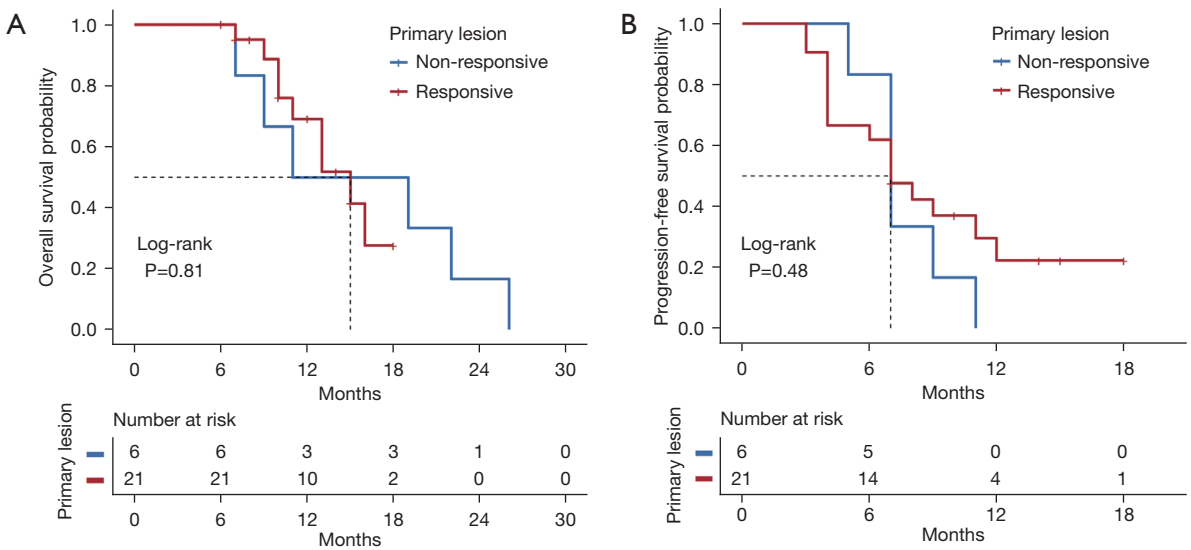

Figure 4 Comparison of Kaplan-Meier survival curves of OS and PFS time between primary gallbladder lesions with and without response. (A) In patients with primary lesions achieved response (CR or PR), the median OS 15.0 months (range, 11–NA months) compared with 15.0 months (range, 9–NA months) in patients exhibited nonresponse (SD or PD) (P=0.809). (B) In patients with primary lesions achieved response, the median PFS was 7 months (range, 4–NA months) compared with 7 months (range, 7–NA months) in patients exhibited nonresponse (P=0.447). OS, overall survival; PFS, progression-free survival; CR, complete response; PR, partial response; NA, not applicable; SD, stable disease; PD, progressive disease.

These results suggest that remission of liver metastasis appears to be more beneficial for long-term survival.

Successful conversion to resection

Six patients in our cohort were successfully converted to resection (22.2%). Cholecystectomy plus regional lymphadenectomy (groups 8, 12, 13a, and 16a2) was routinely performed. Among the patients, two received a right hepatectomy, one received a left hepatectomy plus partial resection of segment 5, one received a resection of segments 5 and 4b, and two received a wedge resection of the gallbladder bed and a local resection of hepatic lesions. The characteristics are shown in *Table 3*. A representative case is shown in *Figure 6*.

Safety

The median number of cycles of combination therapy was four (range, two to six cycles). No patient died during the treatment. No grade 4 AEs were observed.

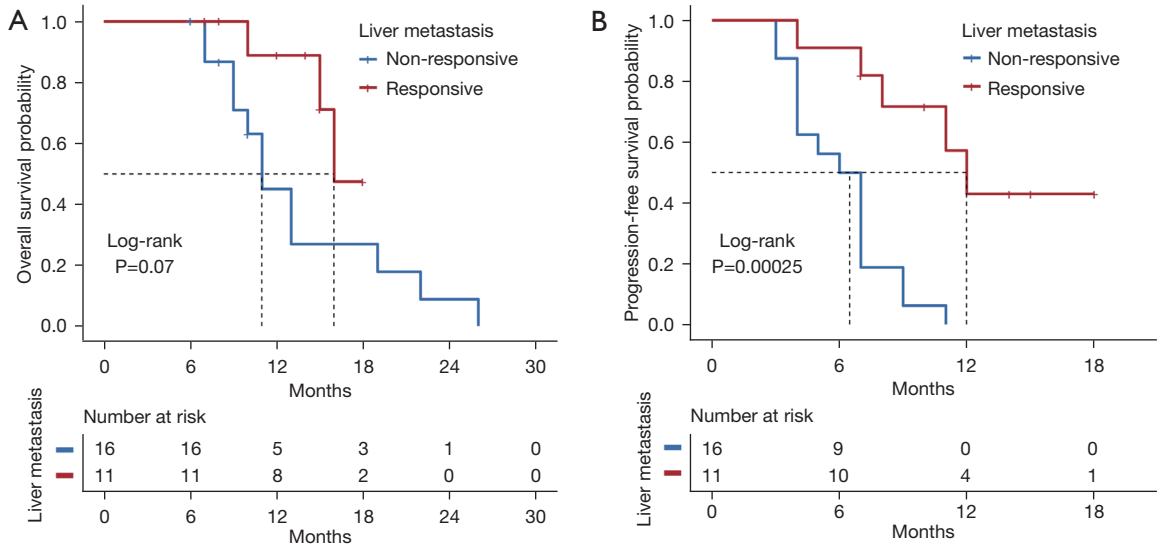

Figure 5 Comparison of Kaplan-Meier survival curves of OS and PFS time between hepatic metastases with and without response. (A) In patients with hepatic metastasis achieved response (CR or PR), the median OS was 16 months (range, 15–NA months) compared with 11 months (range, 10–NA months) in patients exhibited nonresponse (SD or PD) (P=0.070). (B) In patients with hepatic metastasis achieved response, the median PFS was 12 months (range, 8–NA months) compared with 6.5 months (range, 4–9 months) in patients exhibited nonresponse (P<0.001). The decrease of tumor loading on liver intended to have more positive influence on survival. OS, overall survival; PFS, progression-free survival; CR, complete response; PR, partial response; NA, not applicable; SD, stable disease; PD, progressive disease.

All AEs that occurred during combination therapy are summarized in *Table 4*. The main AEs were blood disorders such as neutropenia (92.6%), anemia (44.4%), and thrombocytopenia (55.6%). Other AEs included hypertension (7.4%), hypothyroidism (14.8%), diarrhea (25.9%), vomiting (63.0%), decreased appetite (44.4%), bilirubin elevation (11.1%), ALT elevation (7.4%), and dysesthesia (3.7%). Only six patients experienced grade 3 neutropenia (22.2%). All AEs were alleviated after management.

Subgroup analysis in accordance with the response of hepatic metastasis

Among the patients, 11 (40.7%) patients with hepatic metastasis achieved CR or PR after combination therapy. We preliminarily compared the clinical characteristics between patients who achieved a response (CR or PR) and those who exhibited a non-response (SD or PD) (*Table 5*). The results showed that the gallbladder lesion site, and number and distribution of metastatic lesion were not significantly associated with the response after combination treatment. The preoperative level of CA19-9 (>1,900 U/mL, 36.4% *vs.* 81.3%, P=0.040) and the size of the largest lesion (>5 cm, 27.3% *vs.* 75.0%, P=0.022) were more common in SD and PD groups. A significant decrease in the ^{18}F-FDG SUV value in PET-CT scans was more common in CR and PR groups (decrease >50%, 81.2% *vs.* 18.8%, P=0.002; decrease >90%, 63.6% *vs.* 0.0%, P<0.001).

Discussion

In addition to its anatomical position, GBC is quite different from other BTCs in terms of clinicopathology and molecular insights. Treatments that specifically target GBC remain limited (21). In the present study, we preliminarily investigated the effect of HAIC (FOLFOX regimen) combined with bevacizumab plus a PD-1 inhibitor for treatment of GBC with hepatic oligometastasis. This is an exploratory study in this subgroup of GBC patients. Most patients in this cohort had >1,900 U/mL CA19-9 (66.7%), 22.2% of patients had more than three lesions of hepatic metastasis, and 37.0% patients had liver metastasis spreading over the hemiliver, implying poor prognoses. After combination therapy, they achieved an ORR of 55.6% and a DCR of 85.2%. Median OS was 15.0 months and median PFS was 7.0 months. Six patients (22.2%) were successfully converted to resection. Compared with

Table 3 The characteristics of patients successfully converted to resection

Characteristics	Values
Tumor response	
Partial response	4 (66.7)
Stable disease	2 (33.3)
Cycles of combination therapy	
2	3 (50.0)
3	3 (50.0)
Postoperative adjuvant chemotherapy	
Gemcitabine + albumin-bound paclitaxel	1 (16.7)
Gemcitabine + S1 (tegafur gimeracil oteracil potassium capsule)	2 (33.3)
S1 (tegafur gimeracil oteracil potassium capsule)	3 (50.0)
Type of hepatic resection	
Right hemihepatectomy	2 (33.3)
Left hepatectomy plus partial resection of segment 5	1 (16.7)
Segment 5 and 4b	1 (16.7)
Wedge resection of gallbladder bed and local resection of hepatic lesions	2 (33.3)
Surgical complications	
Pleural effusion	6 (100.0)
Classification complications	
Clavien-Dindo I	5 (83.3)
Clavien-Dindo IIIa	1 (16.7)

Data are presented as n (%).

primary lesions, patients with hepatic metastasis appeared more difficult to achieve remission after the combination therapy (ORR: 40.7% *vs.* 77.8%; P=0.012), but their response appeared to be closely related to prognosis (median OS: 16.0 months in CR and PR groups *vs.* 11.0 months in SD and PD groups, P=0.070; median PFS: 12.0 months in CR and PR groups *vs.* 6.5 months in SD and PD groups, P<0.001). Moreover, the safety and tolerance were acceptable. These results suggest that this strategy has promising prospects.

In this study, hepatic metastasis was defined as a discrete hepatic lesion separate from the primary tumor. Advanced GBC has a tendency to invade the hepatic hilum or hepatoduodenal ligament and often displays lymphatic metastasis. GBC cases with hepatic oligometastasis account for a small proportion of the whole GBC population. These discrete lesions are likely to be of hematogenous origin. Metastatic nodules that spread through a hematogenous route have a poor outcome after resection, irrespective of the type of hepatectomy (22). Furthermore, some of these patients tend to have slightly impaired liver functions without obstructive jaundice and limited tumor involvement without extrahepatic metastasis. Hence, they have not reached uncontrolled systemic metastasis and have the opportunity to be converted to resection after effective treatment. Although they are not the major proportion of unresectable GBC patients, it is reasonable to investigate new strategies because there are limited treatment options at present.

The current frontline chemotherapy for unresectable BTCs including GBC is GC (8). However, the benefit remains poor with an ORR of 21–37% (23). In recent years, HAIC has been a focus as a locoregional chemotherapy. During the HAIC procedure, chemotherapeutic agents are injected directly and continuously into the liver via the hepatic artery. High concentrations of these agents at the tumor site are expected to increase antitumor effects. The first-pass effect results in high local drug concentrations in the liver with minimal systemic distribution, which significantly reduces systemic AEs (24). For GBC with hepatic oligometastasis, HAIC has several potential advantages. Lesions of liver metastasis mainly receive an arterial blood supply (25). Because the cystic artery arises commonly from the right hepatic artery, chemotherapy agents can be administrated to primary gallbladder lesions and hepatic metastasis simultaneously. BTCs are also dense, desmoplastic tumors characterized by a poorly immunogenic tumor microenvironment. These factors contribute to the resistance of GBC to chemotherapy (26). Continuous infusion of chemotherapeutics prolongs contact time and increases the local concentration, which improve the effect. Different from other locoregional treatments, such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radiotherapy, locoregional chemotherapy is also effective for invisible micrometastasis. At present, no studies have reported HAIC therapy using the GC regimen. However, FOLFOX is recommended for neoadjuvant therapy and is a second-line regimen for unresectable and metastatic BTC (27). The FOLFOX protocol has been used for HAIC treatment for a long time, and its safety and efficacy

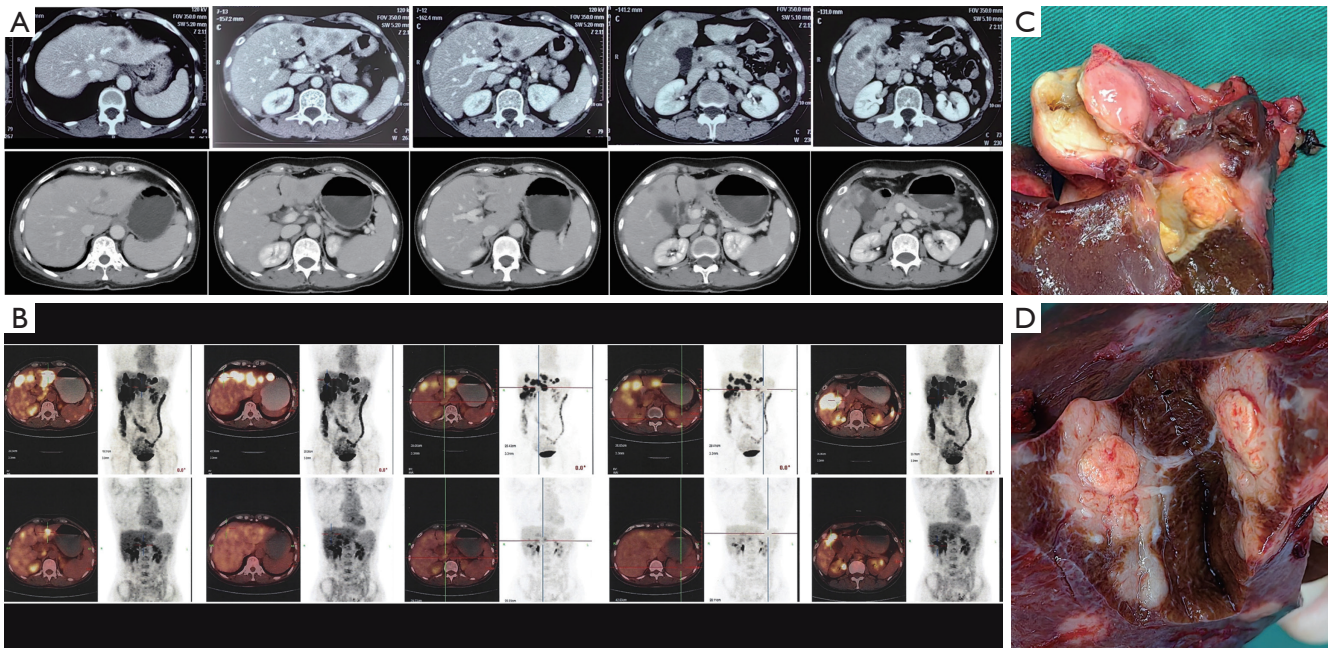

Figure 6 Representative case related to this study. One patient achieved PR after 4 cycles of treatment and received resection eventually. (A) Comparison of CT scan before and after treatment. (B) Comparison of ^{18}F-FDG PET-CT scan before and after treatment. (C) Metastatic lesion with significant decrease of ^{18}F-FDG uptake. (D) Lesion adjacent to gallbladder which still had remarkable ^{18}F-FDG uptake after treatment, a concentric circle structure can be detected in the specimen resected. Pathological examination revealed two metastatic lymph nodes in the hepatic hilar region. This patient had survived for 12 months after resection without recurrence by the end of follow-up (this image is published with the patient/participant's consent). PR, partial response; CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET-CT, positron emission tomography-computed tomography.

have been confirmed in HCC patients (10). Zheng *et al.* investigated HAIC with oxaliplatin and 5-fluorouracil for treatment of advanced GBC. Their study enrolled 26 patients with advanced GBC and found that HAIC was well tolerated and achieved an ORR of 69.2% (14). Therefore, we used FOLFOX for HAIC in this study. Hilar lymph nodes are usually the first site of lymph node metastasis in GBC patients. In theory, the blood supply of hilar lymph nodes comes from the capillary branch of the proper hepatic artery. During the HAIC procedure, we did not embolize the GDA or RGA, which is routinely performed at other centers (10,12,14). This strategy makes chemotherapeutics cover the area around the portal of the liver as much as possible.

Targeted therapy based on specific molecular aberrations, such as fibroblast growth factor receptors-2 (FGFR-2) fusions, isocitrate dehydrogenase-1 (IDH-1) mutations, and human epidermal growth factor-2 (HER-2) amplification or overexpression, has been reported to achieve survival improvement (28). However, these molecular aberrations only occur in a small proportion of GBC patients (26). Anti-angiogenesis therapy is another important field of targeted therapy. Vascular endothelial growth factor (VEGF), the primary growth factor regulating angiogenesis, is over-expressed in 45–75% of BTCs and has been implicated in the control of lymphangiogenesis and lymphatic metastasis in GBC patients (29). In the setting of targeted immunotherapy, VEGF-driven angiogenesis is a logical target. Tyrosine kinase inhibitors (TKIs; e.g., lenvatinib) and monoclonal antibodies (e.g., bevacizumab) are the main choice of anti-angiogenic drugs. Several studies have reported the efficacy and safety of a PD-1 inhibitor plus lenvatinib for advanced GBC with an ORR of 32.3% (9,30). In fact, bevacizumab is more widely used. In the setting of targeted immunotherapy, bevacizumab combined with a PD-1/PD-L1 inhibitor have achieved encouraging results in HCC patients (31). Notably, bevacizumab combined with a PD-1/PD-L1 inhibitor has achieved anti-tumor efficacy in hepatocellular-cholangiocarcinoma (32), which implies effectiveness against BTC. Case reports have shown their

Table 4 Treated related adverse events observed in enrolled patients

Adverse events	Total (n=27)	Grade 1–2	Grade 3
Blood and lymphatic disorders			
Neutropenia	25 (92.6)	19 (70.4)	6 (22.2)
Anemia	12 (44.4)	12 (44.4)	0
Thrombocytopenia	15 (55.6)	15 (55.6)	0
Cardiac disorders			
Hypertension	2 (7.4)	2 (7.4)	0
Endocrine disorders			
Hypothyroidism	4 (14.8)	4 (14.8)	0
Gastrointestinal disorders			
Vomiting	17 (63.0)	17 (63.0)	0
Diarrhea	7 (25.9)	7 (25.9)	0
Decreased appetite	12 (44.4)	12 (44.4)	0
Hepatobiliary disorders			
Bilirubin elevation	3 (11.1)	3 (11.1)	0
ALT elevation	2 (7.4)	2 (7.4)	0
Nervous system disorders			
Dysesthesia	1 (3.7)	1 (3.7)	0

Data are presented as n (%). ALT, alanine aminotransferase.

potential value for GBC treatment (18,33). Sintilimab is a PD-1 inhibitor, which is often used in China. Bevacizumab plus sintilimab have achieved encouraging results in the treatment of HCC (34). Hence, we evaluated bevacizumab combined with sintilimab as a targeted immunotherapy in this study.

Synergies between targeted therapy, immunotherapy, and chemotherapy have been a research focus. Gemcitabine and cisplatin plus immunotherapy show promising efficacy (ORR: 26.7–29%, median OS: 12.7–12.8 months) and acceptable safety in patients with advanced BTC (6,7). In a single arm study, the combination of toripalimab (PD-1 inhibitor), lenvatinib, gemcitabine, and oxaliplatin achieved an encouraging ORR (80%) in advanced intrahepatic cholangiocarcinoma (ICC) patients and exhibited satisfactory safety (35). Therefore, we believe that HAIC combined with bevacizumab plus a PD-1 inhibitor has the potential for GBC treatment. No grade 4 AEs were observed in this study, and all AEs were alleviated after management. Mechanism of synergies between different treatment approaches have also been explored. Anti-VEGF targeted therapies enhance the effect of PD-1 inhibitor by reversing VEGF-mediated immunosuppression and promoting T-cell infiltration in tumors (11). Tumor cells are killed by locoregional chemotherapy and release more specific antigens which were captured by antigen-presenting cells and promote the effect of PD-1. Chemotherapeutic agents have also been shown to induce immunomodulatory effects (15,16). Six patients (22.2%) were successfully converted to resection. The only curative treatment for GBC is radical resection. On the topic of conversion therapy for GBC patients, the optimal treatment strategy remains controversial. Most studies have adopted treatments for advanced BTC or pancreatic cancer (21), and studies of GBC are limited. Our study provides potential new ideas for conversion therapy of unresectable GBC patients.

Compared with primary gallbladder lesions, we found that patients with hepatic metastasis appeared to have more difficulty achieving remission after the combination therapy, but their response appeared to be closely related to the prognosis. The size and number of hepatic metastases often exceed those of the primary lesion. Larger metastatic

Table 5 Comparison of clinical data between patients with hepatic metastasis achieved response and exhibited nonresponse

Clinical data	Hepatic metastasis		P value
	Achieved response (n=11)	Without response (n=16)	
Age >60 years	8 (72.7)	12 (75.0)	>0.999
Gender			0.448
Female	3 (27.3)	7 (43.8)	
Male	8 (72.7)	9 (56.3)	
ECOG score			>0.999
0	10 (90.9)	15 (93.8)	
1	1 (9.1)	1 (6.3)	
CA19-9			0.040
>1,900 U/mL	4 (36.4)	13 (81.3)	
CA19-9 decrease[†]			
>90%	7 (70.0)	6 (37.5)	0.226
Site of gallbladder cancer			0.692
Peritoneal side	0	0	
Hepatic side	8 (72.7)	10 (62.5)	
Diffused	3 (27.3)	6 (37.5)	
Number of liver metastasis			>0.999
1–3	9 (81.8)	12 (75.0)	
>3	2 (18.2)	4 (25.0)	
Metastasis involvement			>0.999
Limited to hemiliver	7 (63.6)	10 (62.5)	
Extended to hemiliver	4 (36.4)	6 (37.5)	
Largest size of metastasis >5 cm	3 (27.3)	12 (75.0)	0.022
^{18}F-FDG SUVmax decrease[‡]			
>50%	9 (81.2)	3 (18.8)	0.002
>90%	7 (63.6)	0	<0.001
Response of metastatic lymph nodes	n=5	n=4	–
PR	4 (80.0)	2 (50.0)	
SD	1 (20.0)	1 (25.0)	
PD	0	1 (25.0)	

Table 5 (*continued*)

Table 5 (*continued*)

Clinical data	Hepatic metastasis		P value
	Achieved response (n=11)	Without response (n=16)	
Preoperative laboratory test			
WBC (×10^9/L)	7.8 [3.9–10.5]	6.39 [3.1–8.1]	0.110
HGB (g/L)	109 [90–128]	122 [84–140]	0.054
PLT (×10^9/L)	271 [245–339]	227.5 [135–315]	0.054
PT (s)	12.1 [11.1–13.4]	11.9 [10.2–13.8]	0.512
TBIL (μmol/L)	10.6 [6.8–26.9]	11.7 [6.8–40.1]	0.790
ALB (g/L)	34.9 [32.3–39.9]	37.0 [31.1–41.1]	0.110
ALT (U/mL)	53.0 [10.7–111.7]	30.4 [13.3–99.3]	0.577
GGT (U/mL)	90.1 [65.1–1,932.0]	110.2 [31.3–662.9]	0.942
Creatinine (mmol/L)	62.0 [51.4–92.0]	70.5 [57.8–98.1]	0.440

Data are presented as n (%), n or median [range]. †, there was one patient with no elevation in CA19-9 level who was excluded from this analysis; ‡, the ^{18}F-FDG SUVmax value was the maximum value of lesion in delay phase during PET-CT scan. ECOG, eastern cooperative oncology group; CA19-9, carbohydrate antigen 19-9; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PR, partial response; SD, stable disease; PD, progressive disease; WBC, white blood cells; HGB, hemoglobulin; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; GGT, gamma-glutamine transpeptidase; SUV, standard uptake value; PET, positron emission tomography; CT, computed tomography.

nodules make it difficult for drugs to enter the tumor, resulting in poor treatment efficacy. Further analysis of our cohort showed that large lesions of >5 cm were associated with a poor response of hepatic metastasis. A poor response of hepatic metastasis also indicated that tumors were refractory and more likely to spread through hepatic veins. Additionally, lesions of hepatic metastasis were more likely to invade the blood vessels and bile ducts in the liver hilum, resulting in deterioration of liver function and discontinuation of treatment.

Further comparison suggested that a preoperative level of >1,900 U/mL CA19-9 and the size of largest lesion being >5 cm were associated with an unsatisfactory response, whereas a significant decrease in ^{18}F-FDG SUVmax was a marker of tumor remission. It is well established that the CA19-9 level is associated with tumor differentiation and strongly correlated to BTC prognosis (36). In our cohort, 66.7% of patients had >1,900 U/mL CA19-9 because all enrolled patients had a poor expected prognosis. A recent study indicated that high levels of ^{18}F-FDG uptake are associated with poor differentiation and microvascular invasion in solid tumors (37). The findings from this study are consistent with the results of previous studies, indicating that a tumor-to-normal liver ratio of >2 (SUV-max of the tumor/SUV-mean of the normal liver) is associated with early tumor progression following PD-L1 inhibitor plus bevacizumab treatment (38). As a metabolic parameter, the significant decrease in ^{18}F-FDG uptake following combination therapy is indicative of necrosis in tumors. Moreover, new extrahepatic metastasis can be detected by a whole-body PET-CT scan, which is crucial to evaluate the treatment response. Hence, in addition to CT/MRI-based evaluation criteria, ^{18}F-FDG SUV and CA19-9 may be valuable biomarkers for accurate assessment of the treatment response.

This pilot study has several limitations. This is a retrospective study with a small sample size, and selective bias was inevitable. Additionally, multivariate analysis was not suitable because of the small sample size. Further research with larger sample sizes is needed to determine the long-term benefit of combination therapy. This study also did not compare the combination therapy with other potential strategies, such as chemotherapy or immune-targeted therapy. Moreover, only a small part proportion of patients with unresectable GBC can potentially benefit from this combination therapy.

Conclusions

HAIC combined with bevacizumab plus a PD-1 inhibitor has promising prospects for the treatment of GBC with hepatic oligometastasis. This study suggests that primary gallbladder lesions have a higher response rate, but the response of hepatic metastasis has more influence on the survival outcome. ^{18}F-FDG uptake and CA19-9 have value as predictors of the treatment response. To validate the current findings, further research should include a randomized clinical trial to assess the safety and effectiveness of this treatment approach.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-816/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-816/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the Ethics Committee of the Sixth Medical Center of Chinese PLA General Hospital (No. HZKY-PJ-2023-44). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All treatment decisions were made at the patient's discretion with informed consent.

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