Original Article

Hepatic arterial infusion chemotherapy for hepatocellular carcinoma refractory to transarterial chemoembolization: exploring the influence of prior transarterial chemoembolization and additional transarterial chemoembolization on survival outcomes

Phan Nhan Hien[1,2]^, Ho Jong Chun[1]^, Jung Suk Oh[1]^, Su Ho Kim[1]^, Byung Gil Choi[1]^

[1]Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Radiology Centre, Hanoi Medical University Hospital, Hanoi, Viet Nam

Contributions: (I) Conception and design: PN Hien, HJ Chun; (II) Administrative support: PN Hien, HJ Chun, JS Oh; (III) Provision of study materials or patients: HJ Chun, JS Oh, SH Kim, BG Choi; (IV) Collection and assembly of data: PN Hien, HJ Chun; (V) Data analysis and interpretation: PN Hien, HJ Chun; (VI) Manuscript writing: All authors; (VII) Final approval of al manuscript: All authors.

Correspondence to: Ho Jong Chun, MD, PhD. Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seochogu, Seoul 06591, Republic of Korea. Email: hojongchun@gmail.com.

Background: The selection of an efficacious treatment modality for patients with hepatocellular carcinoma (HCC) diagnosed as refractory to transarterial chemoembolization (TACE) presents numerous challenges. In addition to systemic therapies, hepatic arterial infusion chemotherapy (HAIC) may serve as an alternative option. However, it is imperative to identify patients who are appropriate candidates for HAIC to confer a survival benefit. Our study aimed to evaluate the impact of the number of TACE sessions prior to HAIC treatment and the addition of TACE during HAIC on the survival of HCC patient's refractory to TACE.

Methods: This retrospective study included 82 patients with HCC refractory to TACE (mean age 60.5 years, 75 males). Survival analysis was conducted using the Kaplan-Meier method, with comparison between two groups via the log-rank test; the Cox regression model was utilized to identify factors influencing survival.

Results: The overall response rate (ORR) was observed to be 29.3%, with a disease control rate (DCR) of 56.1%. Patients receiving more than four TACE sessions prior to HAIC exhibited a significantly poorer survival prognosis compared to those receiving fewer than four TACE sessions, with a hazard ratio (HR) of 0.151 (P=0.02). The median overall survival (OS) was markedly different, being 3.4 (range, 0.5–13.6) months for the former group and 14 (range, 8.5–19.5) months for the latter (P=0.01). Furthermore, patients undergoing additional TACE while receiving HAIC treatment demonstrated improved survival outcomes compared to those who did not, with an HR of 0.491 (P=0.02); the respective OS for these groups was 14 (range, 3.6–14.4) and 6.7 (range, 2.8–11) months (P=0.02).

Conclusions: HAIC can be a suitable alternative treatment for HCC patient's refractory to TACE. For those with a history of more than 4 TACE sessions, other alternative treatments should be considered. The addition of TACE during HAIC treatment may extend patient OS time, provided it is balanced with maintaining safe liver function.

Keywords: Hepatocellular carcinoma (HCC); refractory; transarterial chemoembolization (TACE); hepatic artery infusion chemotherapy (HAIC); survival outcome

^ ORCID: Phan Nhan Hien, 0000-0001-7032-5730; Ho Jong Chun, 0000-0003-4512-6152; Jung Suk Oh, 0000-0003-2709-4935; Su Ho Kim, 0000-0002-2217-009X; Byung Gil Choi, 0000-0002-2950-2069.

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Introduction

In recent years, there has been a significant transformation in the treatment strategies for hepatocellular carcinoma (HCC) patients. The advent of new systemic treatment agents has introduced a variety of options, thereby extending the survival of these patients. Nevertheless, transarterial chemoembolization (TACE) remains the primary treatment choice for patients with non-resectable and intermediate-stage HCC (1). The impact of TACE on tumor control and patient survival has been affirmed over a prolonged period (2).

In HCC patients, the repetition of TACE is often necessary to achieve the best tumor response. However, there are patients who do not respond to TACE, leading to disease progression or metastasis. The concept of TACE failure-refractory was first recognized by the Japan Society of Hepatology (JSH) in 2014. In response to this, alternative and combination treatments have been explored for TACE-refractory patients (3-5). Approaches such as switching from TACE to systemic therapies have been utilized by some authors. Other options, including transarterial radioembolization (TARE), balloon-assisted TACE (B-TACE), and hepatic arterial infusion chemotherapy (HAIC), have also been reported (6-8).

HAIC has emerged as an efficacious alternative treatment for patients with advanced-stage HCC in several East Asian nations (9,10). In the research conducted by Kim *et al.*, a comparison between HAIC and the combination of atezolizumab plus bevacizumab (AB) for advanced-stage HCC showed similar effectiveness in terms of overall survival (OS) and progression-free survival (PFS) (11). The Japan Society of Hepatology (JSH) has also endorsed HAIC for patients with TACE-refractory HCC, particularly those exhibiting impaired liver function, a frequent complication following multiple TACE procedures. Given the lack of uniform treatment criteria for HCC patients diagnosed as refractory to TACE, HAIC can be a suitable alternative treatment option for patient's refractory to TACE (12-14). However, the additional survival time conferred by HAIC treatment for these patients often falls short of 10 months, underscoring the need for careful selection of appropriate candidates (12,15). Our study is focused on identifying factors that influence the extended survival of these patients, centering on their history of TACE procedures and evaluating the necessity of additional TACE in HAIC treatment for TACE-refractory HCC patients. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-1006/rc).

Highlight box

Key findings

- Hepatic arterial infusion chemotherapy (HAIC) can be a suitable alternative treatment for hepatocellular carcinoma (HCC) patient's refractory to transarterial chemoembolization (TACE). For those with a history of more than four TACE sessions, other alternative treatments should be considered. The addition of TACE during HAIC treatment may extend patient overall survival time, provided it is balanced with maintaining safe liver function.

What is known and what is new?

- Numerous studies have employed various methods to treat HCC refractory to TACE. However, there remains a lack of consensus in treatment recommendations. In addition to systemic therapy, HAIC has emerged as an alternative treatment option. Nevertheless, the extension in survival time is still limited.
- In this study, we discovered the influence of the number of TACE procedures before HAIC treatment, as well as the impact of additional TACE during HAIC therapy, on patient survival.

What is the implication, and what should change now?

- Early management of patients with HCC refractory to TACE is crucial, requiring the selection of optimal treatment strategies that balance liver function preservation and maximal tumor response.

Methods

Study population

We conducted the study on 82 HCC patients in Seoul St. Mary's Hospital who were refractory to TACE and subsequently managed with HAIC, covering the period from 2010 to 2021. The retrospective study was approved by the Institutional Review Board of the Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea (No. KC23RISI0417). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the study, the requirement for informed consent was waived. Data

acquisition was finalized in February 2023. Patients were confirmed with HCC either through pathological examination or imaging techniques including contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) scans. According to the JSH 2021 criteria for identifying HCC refractory to TACE, including tumor mass with residual contrast uptake ≥50% or increased number of lesions in the liver compared to previous TACE (on CT/MRI images acquired 1–3 months after completion of at least two TACE procedures), or macrovascular invasion or extrahepatic spread, or tumor maker not immediately decreased after TACE or only minimally decreased and then continued to increase (16). Our study considered patients eligible if they: (I) satisfied the JSH guideline for TACE-resistant HCC; (II) were older than 18; (III) had at least one quantifiable lesion observable on CT/MRI; and (IV) exhibited an Eastern Cooperative Oncology Group performance status score of 2 or less. Candidates were excluded if they: (I) lacked follow-up information post-treatment; (II) were 18 years old or younger; (III) had a recent (within 5 years) history of other malignant conditions; or (IV) died due to other documented causes.

Treatment protocol

The procedure was implemented under local anesthesia, accessing either through the right femoral or the left subclavian artery. Utilizing the Seldinger technique, a catheter was introduced into the arterial lumen over a 0.035-inch guidewire (Terumo, Tokyo, Japan). Angiography was performed on celiac, superior mesenteric, and extrahepatic arteries that fed the tumor, if present, to assess the anatomy of the hepatic blood supply and tumor arteries. Before HAIC port implantation, collateral branches from extrahepatic arteries were occluded to enhance treatment efficacy. Microcoils (Tornado, Cook, USA) were used to embolize the right gastric artery to prevent chemotherapeutic agents from refluxing into the stomach. A 5 Fr port and catheter (Celsite, B. Braun Medical, Pennsylvania, USA) were placed in the common hepatic artery before the distal end of the catheter was fixed to the gastroduodenal artery using microcoils. After each cycle of HAIC therapy, 3,000–5,000 U of heparin were injected into the port to prevent catheter occlusion (17).

Chemotherapy

Epirubicin-cisplatin-5-fluorouracil (ECF) chemotherapy regimen was administered roughly monthly. This regimen encompassed a dose of 35 mg/m^2 of epirubicin on the first day, succeeded by a dose of 60 mg/m^2 of cisplatin over a duration of 2 hours on the second day, and a dose of 500 mg/m^2 of 5-fluorouracil administered over a span of 5 hours on the first and third days (17).

Study parameters

Upon diagnosing a patient with TACE-refractory HCC, the treatment of choice was HAIC. Data on TACE conditions, including the number of TACE treatments, number of TACE non-responses, time from the first non-response TACE to HAIC treatment, and JSH-based criteria for diagnosing refractory to TACE, were recorded. Barcelona Clinic Liver Cancer (BCLC) stage was classified based on conditions at the time of HAIC preparation. The indices of general condition and liver function, such as Child-Pugh score, Albumin-Bilirubin (ALBI) score (18), were collected using established formulas. Tumor imaging characteristics including number, size, and portal vein tumor thrombosis (PVTT) classification were recorded (19).

In this study, we evaluated tumor response based on the modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria, utilizing contrast-enhanced CT/MRI imaging. Tumor response, as recorded in our research, refers to the best observed outcome from the initiation of HAIC until the patient's demise or loss of follow-up. The survival time documented includes OS and PFS, defined respectively as the duration from the commencement of HAIC treatment until the patient's death or loss of follow-up, and the time until disease progression or death, whichever occurs first.

Statistical analysis

In our research, continuous variables are reported using means and standard deviations, while categorical variables are presented as frequencies or percentages. The Kaplan-Meier method is employed to calculate survival time, with differences between study groups assessed using the log-rank test. The Cox regression model is utilized to analyze factors influencing patient survival. All statistical analyses are performed using SPSS version 26.

Results

Baseline characteristics

Our study included 82 patients diagnosed with HCC

refractory to TACE based on the JSH 2021 criteria. Their mean age was 60.5±10.7 years. There were 75 (91.5%) males. Six (7.3%) patients had received surgical resection or liver transplantation due to HCC prior to this study. The majority (90.2%) of patients had well-preserved liver function classified as Child-Pugh A, while the rest were classified as Child-Pugh B. There was no case of Child-Pugh C. PVTT was present in 53 (64.6%) patients, mostly Vp1–2 (42.7%). The average number of TACE sessions before the HAIC treatment was 5.3±3.5. Twenty-six (31.7%) patients received additional TACE during the HAIC treatment. The most common cause of TACE refractoriness was poor response of the tumor to treatment (75.6%), while the least common cause of TACE refractoriness was extrahepatic spread (6.1%) (*Table 1*).

Tumors responses and survival outcomes

Of all patients, 4 (4.9%) achieved complete response (CR), 20 (24.4%) achieved partial response (PR), 22 (26.8%) had stable disease (SD), and 36 (43.9%) had progression disease (PD). Twenty-four (29.3%) patients showed objective response (OR), while 46 (56.1%) patients had disease control (DC) (*Table 2*). The mean OS in our study was 14.0 months, with a median OS of 9.9 (range, 8.7–11) months. The mean

Table 1 Baseline characteristics of study subjects

Characteristics	Value
Age (years)	60.5±10.7
Sex	
Male	75 (91.5)
Female	7 (8.5)
Child-Pugh score	
A	74 (90.2)
B	8 (9.8)
C	0
BCLC stage	
A	0
B	49 (59.8)
C	33 (40.2)
AFP (ng/mL)	333.4 (1.7–348,100)
PIKA-II (ng/mL)	1,075 (5–88,655)
Albumin (g/dL)	3.4±0.5
AST (U/L)	72.6±75.9
ALT (U/L)	56.4±112.7
CRP (mg/L)	1.6±2.3
PVTT	
Vp0	29 (35.4)
Vp1	11 (13.4)
Vp2	24 (29.3)
Vp3	16 (19.5)
Vp4	2 (2.4)
Tumor size (mm)	72.5±34.3
Tumor number	6.2±6.6
Number of prior TACE	5.3±3.5
Number of TACE-refractory	2.65±1.3
Additional TACE after HAIC[#]	26 (31.7)
Types of TACE-refractories	
Poor responses of the target tumor	62 (75.6)
New tumor lesions	42 (51.2)
Extrahepatic metastasis	5 (6.1)
Vascular invasion	34 (41.5)
Continuously elevated tumor markers	38 (46.3)

Data are presented as mean ± standard deviation or median (interquartile range) or n (%). #, the patient received TACE during the HAIC treatment. Vp0, no PVTT; Vp1 includes the presence of PVTT distal to the second-order branches of the portal vein; Vp2 is invasion of the second order branches of the portal vein; Vp3 is the presence of the PVTT in the first-order branch; Vp4 includes PVTT in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both). BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; PIKA-II, prothrombin induced by vitamin K absence-II; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

Table 2 Univariate and multivariate analyses of factors associated with patients' overall survival

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age (years)	0.996	0.975–1.017	0.70			
Sex						
Male	1					
Female	0.984	0.424–2.283	0.96			
Child-Pugh score						
5	1			1		
6	0.248	0.071–0.865	0.02	0.859	0.138–5.355	0.87
7	0.279	0.079–0.978	0.05	1.072	0.171–6.718	0.94
8	0.396	0.085–1.852	0.23	1.105	0.142–8.585	0.92
BCLC stage	0.631	0.389–1.022	0.06			
AFP (ng/mL)	1	1.000–1.000	0.03	1	1.000–1.000	0.12
PIKA-II (ng/mL)	1	1.000–1.000	0.18			
Albumin (g/dL)						
>3	1					
≤3	2.892	1.112–6.396	0.003	2.363	1.341–4.160	0.006
AST (U/L)						
≤40	1					
>40	1.011	1.005–1.017	<0.001	1.005	1.001–1.009	0.008
ALT (U/L)	0.998	0.993–1.002	0.22			
ALBI score	1.586	1.008–2.496	0.04	0.552	0.239–1.273	0.16
CRP (mg/L)						
≤3	1					
>3	1.135	1.015–1.268	0.02	1.168	1.011–1.351	0.03
PVTT						
Vp0	1					
Vp1–2	0.957	0.509–1.800	0.89			
Vp3–4	1.039	0.559–1.931	0.90			
Tumor size	1.002	0.994–1.009	0.69			
Tumor number						
1–4	1					
>4	1.042	1.006–1.079	0.02	1.072	1.026–1.120	0.002
Number of prior TACE						
2–4 sessions	1					
>4 sessions	1.086	1.007–1.172	0.03	1.521	1.054–2.196	0.02
Additional TACE during HAIC	0.438	0.258–0.743	0.002	0.491	0.268–0.899	0.02

Vp0, no PVTT; Vp1 includes the presence of PVTT distal to the second-order branches of the portal vein; Vp2 is invasion of the second order branches of the portal vein; Vp3 is the presence of the PVTT in the first-order branch; Vp4 includes PVTT in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both). BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; PIKA-II, prothrombin induced by vitamin K absence-II; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ABLI score, Albumin-Bilirubin score; CRP, C-reactive protein; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; CI, confidence interval.

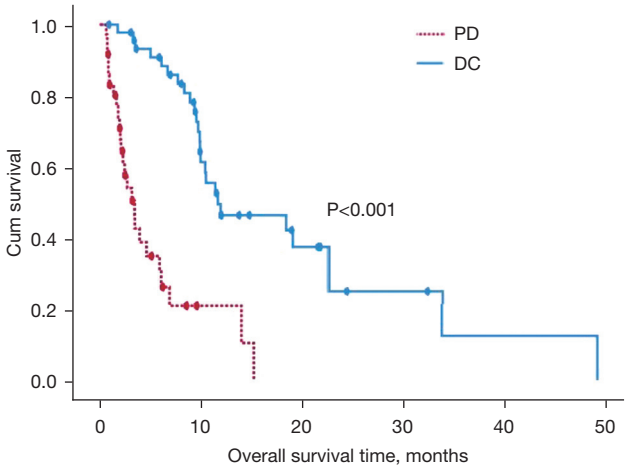

Figure 1 Kaplan-Meier OS analysis: the OS for the DC group was 11.7 (range, 1.9–21.4) months compared to 3.4 (range, 2.2–4.6) months for the PD group, with a P value of <0.001. OS, overall survival; DC, disease control; PD, progressive disease.

PFS time was 8.4 months, with a median PFS of 4.7 (range, 3.4–5.9) months. The median OS was 11.7 (range, 1.9–21.4) months for the DC group and 3.4 (range, 2.2–4.6) months for the PD group (*Figure 1*).

Factors predictive of survival outcomes

In the multivariate analysis, six factors significantly (P<0.005) affecting OS were albumin serum level ≤3 g/dL [hazard ratio (HR): 2.363, P=0.006], aspartate aminotransferase (AST) >40 U/L (HR: 1.005, P=0.008), C-reactive protein (CRP) >3 mg/L (HR: 1.168, P=0.03), tumor number >4 (HR: 1.072, P=0.002), number of TACE sessions prior to HAIC port implantation >4 (HR: 1.521, P=0.02), and additional TACE after HAIC (HR: 0.491, P=0.02) (*Table 2*). The OS for the group receiving 2–4 prior TACE sessions before HAIC and the group receiving more than 4 TACE sessions were 14 (range, 8.5–19.5) and 3.4 (range, 0.5–13.6) months, respectively, showing a statistically significant difference with a P value of 0.01 (*Figure 2A*). In the groups receiving additional TACE during HAIC and those not receiving additional TACE, the OS was 14 (range, 3.6–24.4) and 6.7 (range, 2.8–11) months, respectively, with a P value of 0.02 (*Figure 2B*).

Discussion

Selecting treatments for patients with advanced HCC, especially those diagnosed as refractory to TACE, remains a challenging endeavor, marked by variability in current clinical practices. The response of the tumor emerges as a pivotal determinant of patient survival. For instance, in Kim's study, the survival period for patients exhibiting a positive tumor response was substantially longer than for non-responders: 22.1 *vs.* 6.5 months (15). Our study aligns with these findings, demonstrating a median OS of 11.7 (range, 1.9–21.4) months in the DC group, compared to 3.4 (range, 2.2–4.6) months in the PD group, with a significant P value of <0.001. In addition to tumor quantity and morphology, and clinical indicators like serum albumin, AST levels, and CRP, which are consistent with other HCC studies; our research identified a correlation between the number of TACE sessions prior to HAIC and patient prognosis (15,20). Specifically, patients who underwent more than 4 TACE sessions before HAIC exhibited a poorer prognosis than those who received 2–4 TACE sessions (HR: 1.521, P=0.02), with corresponding survival times of 3.4 (range, 0.5–13.6) and 14 (range, 8.5–19.5) months (P=0.01). Furthermore, our study indicates that additional TACE during HAIC can significantly extend survival (HR: 0.491, P=0.02), with the OS for patients receiving additional TACE during HAIC versus those who did not being 14 (range, 3.6–24.4) and 6.7 (range, 2.8–11) months, respectively (P=0.02).

There are variations in the criteria for diagnosing TACE resistance across different guidelines, but generally, it is identified by at least two unsuccessful TACE sessions or the emergence of vascular invasion or distant metastasis. The implementation of scoring systems for the diagnosis or prediction of TACE resistance may facilitate earlier detection. Repeated TACE not only potentially worsens hepatic function in patients but also may decrease the efficacy of chemotherapeutic agents, especially in cases of sarcomatous transformation, complicating the selection of alternative treatments (21). Our study underscores that patient with TACE resistance, particularly those with a history of more than four prior TACE sessions, should consider alternative treatment modalities such as systemic therapy. In Onishi's study, patients who underwent more than three TACE sessions before HAIC typically exhibited shorter OS compared to other patients (22).

The combination therapy of TACE and HAIC has demonstrated not only an increase in tumor response rates but also an extension in patient survival (*Figure 3*). In Liu's study, which investigated the synergy of TACE and HAIC in treating advanced HCC, this combined approach was

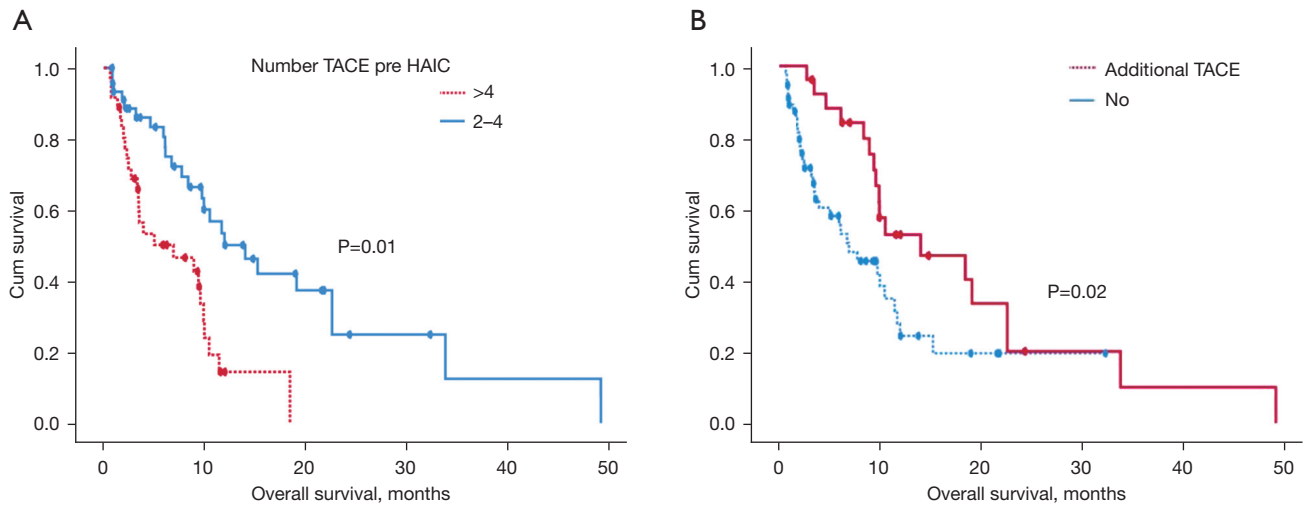

Figure 2 Kaplan-Meier OS analysis comparing: (A) the OS of the group that underwent 2–4 prior TACE treatments before HAIC treatment and the group with more than four sessions TACE treatments was 14 (range, 8.5–19.5) *vs.* 3.4 (range, 0.5–13.6) months, respectively, with a P value of 0.01; (B) the OS of the group receiving additional TACE during HAIC treatment and the group without additional TACE was 14 (range, 3.6–24.4) *vs.* 6.7 (range, 2.8–11) months, respectively, with a P value of 0.02. TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; OS, overall survival.

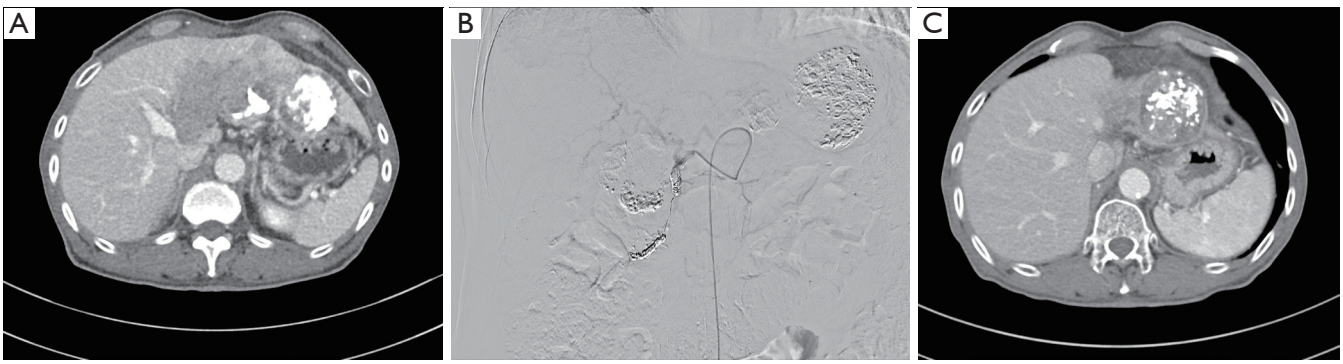

Figure 3 A 67-year-old male patient with a history of hepatitis B and a 5-cm HCC in the left hemisphere was diagnosed with HCC refractory to TACE after receiving two TACE sessions: (A) CT imaging revealed an infiltrative HCC mass with left PVTT, and AFP serum level: 931 ng/mL, PIKA-II: 2,685 ng/mL; (B) the patient received treatment with HAIC; (C) after four cycles of HAIC, there was a significant reduction in the size of tumor and PVTT, with normalization of AFP and PIKA-II serum levels. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; PIKA-II, prothrombin induced by vitamin K absence-II; HAIC, hepatic arterial infusion chemotherapy; CT, computed tomography.

identified as an independent factor positively correlating with OS and PFS, without a significant difference in adverse events compared to the group treated with TACE alone (23). Huang's research further supports this, showing that the combination of drug-eluting bead transarterial chemoembolization (DEB-TACE) and HAIC in patients with large HCC resulted in better overall response rate (ORR), PFS, and OS compared to those treated solely with DEB-TACE (24). Our study corroborates these findings, demonstrating that patients receiving additional TACE during HAIC treatment had a longer OS compared to those without additional TACE, thereby highlighting the benefits of integrating TACE. While there are clear benefits in increasing tumor response rates through this combination

therapy, it is crucial to balance these advantages with the need to preserve hepatic function, especially in patients who have undergone multiple TACE procedures previously.

Our study has several limitations. First, the patient cohort size is relatively small. However, the selection of patients who were refractory to TACE was meticulously undertaken following the criteria established by the JSH. Second, owing to the retrospective design of our study, there may be an oversight of some clinical data during the collection process, and the cause of death for some patients may not be clearly ascertained. Third, it is necessary to compare our findings with other treatment modalities, for instance, systemic therapies. Despite these limitations, our study provides additional insights to enhance the effectiveness of HAIC in patient's refractory to TACE. This approach may be applicable when patients are unsuitable for or decline systemic treatments.

Conclusions

In conclusion, HAIC can be a suitable alternative treatment option for patient's HCC refractory to TACE. However, for patients with a history of receiving more than four TACE sessions, exploring other alternative treatment methods is advisable. The addition of TACE during HAIC treatment may provide the benefit of extending patient OS time, provided that this approach is carefully balanced with ensuring liver function remains within safe limits.

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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-23-1006/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-1006/dss

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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-23-1006/coif). All authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea (No. KC23RISI0417). Because of the retrospective nature of the study, the requirement for informed consent was waived.

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