J Chin Med Assoc

ORIGINAL ARTICLE

Combination therapy of sorafenib and drug-eluting bead transarterial chemoembolization for advanced hepatocellular carcinoma with and without hepatic arteriovenous shunt

Pin-Ko Chen[a], Sung-Hua Chiu[a], Ming-Ting Tsai[b], Kai-Hsiang Chang[a], Wei-Chou Chang[a,*], Hsuan-Hwai Lin[c], Cheng-Hsiang Lo[d], Guo-Shu Huang[a], Ping-Ying Chang[e,*]

[a]Department of Radiology, Tri-Service General Hospital, National Defense Medical Center, Taipei, ROC, Taiwan; [b]Department of Medical Imaging, China Medical University Hsinchu Hospital, Hsinchu,Taiwan, ROC; [c]Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC; [d]Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC; [e]Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC

Abstract

Background: To compare the efficacy and safety of combination therapy with sorafenib and drug-eluting bead transarterial chemoembolization (DEB-TACE) in advanced hepatocellular carcinoma (HCC) with or without hepatic arteriovenous shunt (HAVS).

Methods: This retrospective, single-center study enrolled 59 advanced HCC patients treated with combination therapy, of whom 33 (55.9%) patients had HAVS. Tumor response according to the mRECIST criteria was evaluated based on the CT images 1 month after TACE, and changes in the arterial enhancement ratio (AER) of tumors and portal vein tumor thrombosis were also documented. Time-to-progression (TTP), overall survival (OS), and prognostic factors were analyzed. Safety was evaluated with the incidence of TACE-related complications within 6 weeks after TACE.

Results: The tumor response between the two groups showed no significant difference in the objective response rate (69.2% in the group without HAVS vs 60.6% in the group with HAVS, $p = 0.492$) or disease control rate (92.3% vs 87.9%, $p = 0.685$). The two groups showed comparable TTP (4.23 vs 2.33 months, $p = 0.235$) and OS (12.77 vs 12.97 months, $p = 0.910$). A drop in the AER of tumors of more than 20% on post-TACE CT independently predicted better OS. With regard to safety, there was no significant difference between the two groups.

Conclusion: For advanced HCC, combination therapy had equal efficacy and safety in patients with HAVS compared to those without HAVS, indicating that DEB-TACE is an optional and effective treatment in these patients.

Keywords: Carcinoma; Chemoembolization; Hepatocellular; Liver neoplasms; Sorafenib; Therapeutic

1. INTRODUCTION

As hepatocellular carcinoma (HCC) progresses to an advanced stage, it may develop vascular invasion and tumor thrombosis and is commonly accompanied by hepatic arteriovenous shunt (HAVS). HAVS, which includes arterioportal and arteriosystemic shunts, reportedly occurs in 28.8% to 63.2% of HCC patients.[1–3] Transarterial chemoembolization (TACE) has proven to be effective and is considered as a first-line therapy in Barcelona Clinic Liver Cancer (BCLC)-B (intermediate stage) patients.[4] In BCLC-C (advanced stage), systemic therapy rather than TACE is recommended, and the combination of systemic therapy and TACE is often contraindicated in these patients because major portal venous invasion increases the risks of hepatic failure.

Despite the controversy and concerns of potential harm from TACE, recent studies have reported that both conventional TACE (c-TACE) and drug-eluting bead (DEB) TACE (DEB-TACE) can be safely performed in patients with portal vein tumor thrombosis (PVTT) and improve survival.[3,5] In the past, the presence of HAVS was considered a contraindication to TACE[6] because it can cause nontarget embolization of normal liver parenchyma and run-off of chemotherapeutic agents into systemic circulation. With the advancement of interventional radiology, there is accumulating evidence indicating that TACE may be safe and effective in HCC with HAVS.[7–12]

As a novel drug-delivering agent for TACE, DEB-TACE showed higher concentrations of chemotherapeutic agents

*Address correspondence. Dr. Wei-Chou Chang, Department of Radiology, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Chenggong Road, Taipei 114, Taiwan, ROC. E-mail address: weichou.chang@gmail.com (W.-C. Chang); Dr. Ping-Ying Chang, Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Chenggong Road, Taipei 114, Taiwan, ROC. E-mail address: max-chang@yahoo.com.tw (P.-Y. Chang).

Author Contributions: Dr.Wei-Chou Chang and Dr.Ping-Ying Chang contributed equally to this work.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 491-499.

Received June 18, 2021; accepted September 7, 2021.

doi: 10.1097/JCMA.0000000000000696.

delivered into tumors, reduced adverse events and better patient tolerance.[13] DEB-TACE also revealed its superiority compared to cTACE in the treatment of HCC with a hypovascular pattern[14] and extrahepatic collateral blood supply.[15] However, at present, the role of DEB-TACE in treating advanced HCC with HAVS remains undetermined.

The purpose of this study was to evaluate the efficacy and safety of DEB-TACE with a modified embolization method and to analyze the imaging prognostic factors for advanced HCC with HAVS.

2. METHODS

2.1. Study design

This was a retrospective single-center study following the protocol and principles of the Declaration of Helsinki and was in accordance with the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice. Institutional Review Board (IRB) approval was obtained by Tri-Service General Hospital (1–105-05-158) with a waiver of informed consent, because the waiver or alteration will not adversely affect the rights and welfare of the subjects, and all patient data were protected under the rules of IRB.

2.2. Patients

A computerized search of databases for HCC patients from October 2015 to December 2017 was performed for retrospective chart and image review. Patients (>18 years) with a diagnosis of HCC based on either American Association for the Study of Liver Diseases guidelines,[16] LI-RADS guidelines,[17] or biopsy were included. Inclusion criteria included the following: (1) advanced HCC patients; (2) normal liver or compensated cirrhosis with preserved liver function (Child–Pugh score A or B); (3) adequate renal function (serum creatinine <1.5 times the upper limit of normal); and (4) acceptable performance status (PS 0–1). Exclusion criteria included hepatic tumor burden over 70%, severe coagulopathy, and second primary malignancy. Patients who had undergone radiotherapy or targeted therapy were also excluded.

2.3. Follow-up assessment

Standard follow-up evaluations, including clinical assessment, radiological examination, and laboratory evaluations, were performed during weeks 4 to 6 after treatment initiation and every 8 to 12 weeks thereafter. Patients were enrolled from October 2015, with a cutoff date for follow-up set at February 2018.

2.4. Imaging parameters of HCC, PVTT, and HAVS

An independent diagnostic radiologist implemented quantitative measurements of the target HCCs and PVTT if visible using four-phase dynamic CT before and after the combination treatment. The following baseline imaging parameters were recorded: (1) the greatest diameter of the HCCs; (2) unilobar or bilobar tumor involvement; (3) tumor morphology: ill-defined or well-defined margins; (4) enhancing capsule, defined as an enhanced, sharp border surrounding the mass that persisted in the portal-venous phase or delayed phase; (5) ancillary features of HCCs, including mosaic enhancement, nodule-in-nodular sign, and presence of intratumoral hemorrhage; (6) macroscopic vessel involvement, defined as direct invasion or thrombus of the portal vein, hepatic vein, or inferior vena cava detected macroscopically. PVTT was classified as follows: (1) low-grade PVTT was defined as thrombosis in the second- or lower-order portal vein branches; and (2) high-grade PVTT was defined as thrombosis in the main or first-order portal vein branch.

The mean CT attenuation (Hounsfield unit [H.U.]) on unenhanced and arterial phases of the tumor and PVTT was collected before and after the combination treatment. Attenuation of the target HCC was measured with the selected image having maximal HCC dimension in axial view. Attenuation of PVTT was measured with the most front of the tumor thrombus,[18] and the dimension of the measured area was equal to the thrombus diameter. The arterial enhancement ratio (AER) of the tumor was calculated with the following formulas[19]: $AER_{Tumor} = (HU_{Tart}\text{-}HU_{Tn})/HUTn$, where HU_{Tar} is the H.U. of tumor in the arterial phase, and HU_{Tn} is the H.U. of tumor in the noncontrast phase (Fig 1A–D). AER_{PVTT} was also calculated with this formula. In this study, we defined the treatment response as at least stable by the cutoff value of a 20% decrease in AER_{Tumor} and a 50% decrease in AER_{PVTT} after DEB-TACE treatment.

2.5. Combination therapy of sorafenib and DEB-TACE

Patients were treated with oral sorafenib (Nexavar, Bayer AG) and DEB-TACE. The starting dose of sorafenib was 400 mg orally twice; if there was any drug-related toxicity, treatment discontinuation or a decrease in dose frequency was decided by the gastroenterologist. Sorafenib administration could be continued until disease progression, intolerance of patients, and liver function deterioration.

HCC and HAVS embolization procedures were performed as follows: DEB-TACE, if tolerable, was performed up to two times in the first 3 months (treatment interval: 4-6 weeks). For patients with bilobar disease, the treatment was performed first in the lobe with a higher tumor burden based on CT imaging, and then the other lobe was treated in the next session. All angiographies were performed on an Axiom Multistar system (Siemens). Angiographic evaluation of the superior mesenteric artery was performed routinely in the first DEB-TACE course to outline the portal circulation in the venous phase. Celiac and common hepatic angiography were performed to identify hepatic tumors and HAVS. Subsequently, a microcatheter (Progreat, Terumo) was coaxially inserted into each hepatic branch for superselective angiography to confirm the shunts and tumor-feeding arteries. The tip of the microcatheter was placed into each shunt-feeding artery as close as possible and then targeted the main feeder vessels first if superselective catheterization was possible.

For advanced HCC with low-flow shunt embolization, gelfoam sponges were administered first for shunt embolization before DEB-TACE was performed. The embolization mixture was injected slowly under real-time fluoroscopy until slow flow or hemostasis occurred to induce shunt occlusion. After shunt embolization, DEB-TACE was performed with 30–60 μm HepaSpheres (Merit Medical), and each vial of HepaSpheres (25 mg) was mixed with 50 mg doxorubicin (solubilized in NaCl 0.9% solution) 1 hour before the procedure to maximize the uptake of the chemoagents into the spheres. Then, the loaded HepaSpheres were mixed with 20 mL nonionic contrast to form a homogeneous suspension. The maximum dose administered was 100 mg doxorubicin (loaded with two vials of HepaSpheres). After that, Gelfoam sponges were also used as adjuvant embolizing agents for adequate devascularization.

For moderate- to high-flow shunts, DEB-TACE was performed without embolization of the shunt, and the microcatheter was introduced deeply enough into the tumor-feeding artery that did not supply the shunt. During the injection of DEBs, real-time fluoroscopy helped to confirm that no beads flowed to nontarget areas. After that, Gelfoam sponges were also used as adjuvant embolizing agents for adequate devascularization.

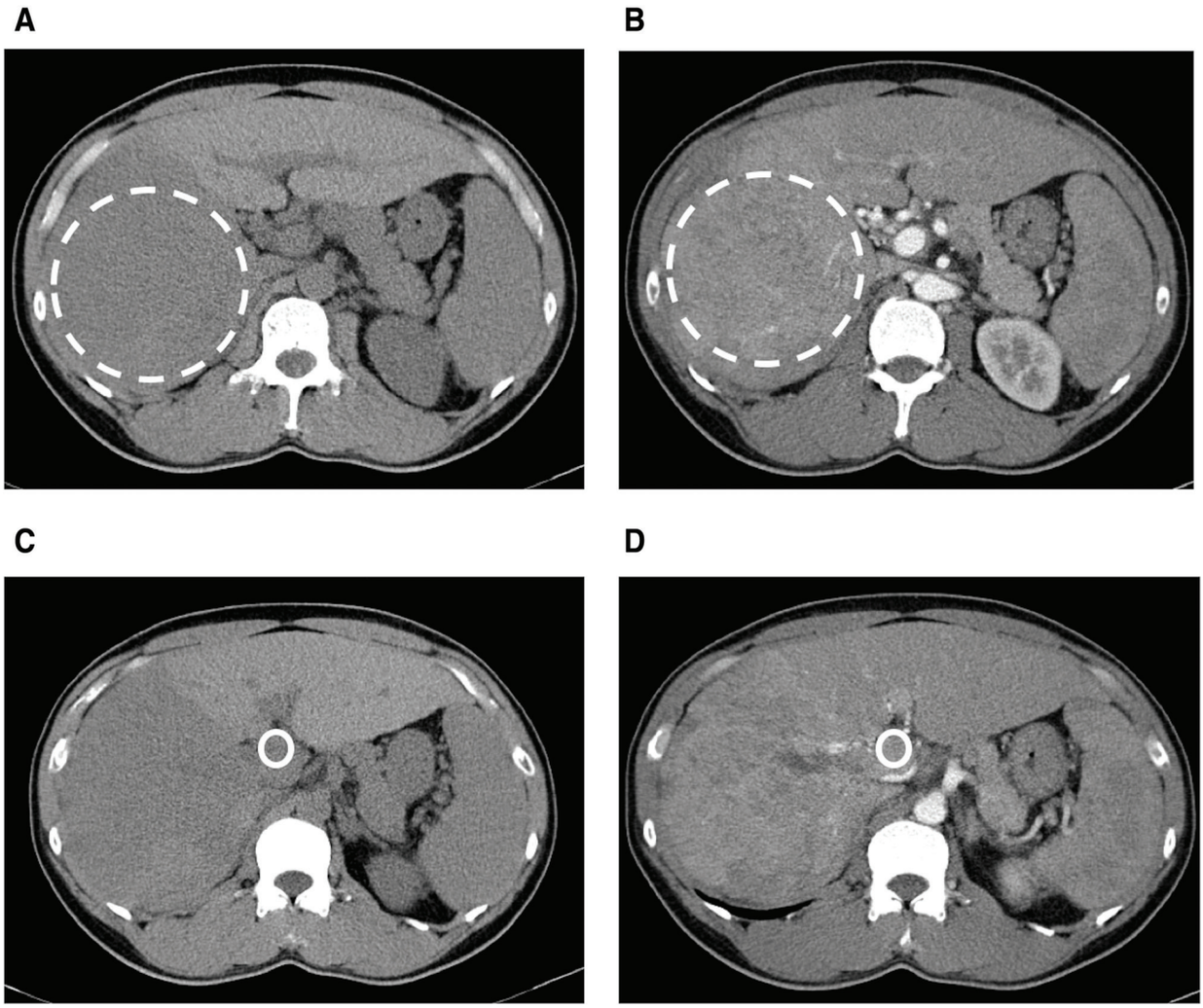

Fig. 1 Infiltrative HCCs with portal vein tumor thrombosis (PVTT) and arterioportal shunting (APS) in a 45-year-old man with HBV-related liver cirrhosis. A and B, For HCCs in the right lobe, the ROI value of lesion attenuation on the unenhanced CT image (A) was 43 HU. On the arterial phase, the ROI value of lesion attenuation was 87 HU. Tumor arterial enhancement ratio (AER) was calculated as (87-43)/43 = 1.02. C and D, For PVTT in the right main portal vein, the ROI value of lesion attenuation on The unenhanced CT image (A) was 42 HU. On the arterial phase, the ROI value of lesion attenuation was 102 HU. AER_{PVTT} was calculated as (102-42)/42 = 1.43. HCC = hepatocellular carcinoma.

2.6. Local tumor response and patient survival

Tumor response was assessed using four-phase dynamic CT imaging at baseline, at 4 weeks after each chemoembolization, and 8 to 12 weeks afterward if there was no evidence of viable residual tumor or newly developed lesions requiring additional chemoembolization. Images were interpreted by an experienced diagnostic radiologist independently who was blinded to the study. Responses were assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria[20] 1 month after each TACE session. TTP and overall survival (OS) were calculated from the date of first TACE treatment to the date of radiographic evidence of disease progression (TTP) or the date of death/last follow-up (OS). Patients who underwent liver transplantation were noted as censored events.

2.7. Safety

Procedure-related hepatotoxicity was assessed based on the development of one of the hepatobiliary severe adverse events as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Hepatotoxicity was recorded if any of the following laboratory data or clinical states was abnormal within 6 weeks after the procedure: elevated serum levels of total bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT); the presence of ascites; or clinical hepatic failure was defined as NCI CTCAE grade 3 to 4.

2.8. Statistical analysis

Statistical analyses were performed with SPSS version 26 (IBM Corporation), and differences were considered significant when $p < 0.05$. The results are expressed as the mean value ± standard deviation for continuous variables, absolute frequencies, and percentage for categorical variables. The metric data were compared with Student's *t* tests. TTP and OS curves were created using the Kaplan–Meier method and compared using log-rank tests. Univariate and multivariate analyses of TTP and OS were performed by Cox regression, and variables identified as

significant in the univariate analysis were incorporated into the multivariate analysis.

3. RESULTS

3.1. Baseline characteristics of the patients

A total of 59 patients with advanced-stage HCC treated with combination therapy of sorafenib and DAB-TACE were enrolled in this study, and baseline patient characteristics are shown in Table 1. Twenty-six patients had no visible HAVS, and the other 33 patients had HAVS. The performance status in both groups was mostly ECOG 1 (69.2% and 66.7%, respectively).

Regarding the pre-TACE imaging factors (Table 2), most of the tumors in both groups were larger than 5 cm (76.9% in the group without HAVS and 84.8% in the group with HAVS). In the group with HAVS, 44.1% of patients had high-grade PVTT, which was significantly higher (p = 0.002) than the group without HAVS (7.7%). Most of the HCCs were nodules or masses in appearance, and less than one-third of HCCs appeared as infiltrative type in both groups (15.4% vs 27.3%, p = 0.274).

3.2. Tumor response after TACE

As presented in Table 3, the volume reduction between the two groups, based on a 30% threshold according to the mRECIST criteria, showed no significant difference (69.2% in the group without HAVS vs 60.6% in the group with HAVS, p = 0.492). The presence of newly developed lesions in the first follow-up imaging studies showed no significant difference between the two groups (30.8% vs 42.4%, p = 0.358).

The tumor response according to the mRECIST criteria is shown in Table 3. There was a statistically significant difference in the tumor response between the two groups (p = 0.03), in which 23.1% of patients in the group without HAVS achieved a complete response compared with no patients in the group with HAVS. Nevertheless, both the objective response rate (ORR) and disease control rate (DCR) revealed no significant difference between the two groups (p = 0.492 and 0.685, respectively).

3.3. Quantitative MDCT analysis of the target HCCs and PVTT

Before combination therapy, AER_{Tumor} between the two groups showed no significant difference (p = 0.874, as shown in Table 4).

Table 1

Baseline patient characteristics

Characteristics	Advanced HCC without HAVS (n = 26)	Advanced HCC with HAVS (n = 33)	p
Age (mean ± SD, years)	64.37 ± 13.95	60.23 ± 13.67	0.252
Sex			0.957
Male	14(46.2)	18(54.5)	
Female	12(53.8)	15(45.5)	
Etiology of cirrhosis			0.497
Hepatitis B	16(61.5)	23(69.7)	
Hepatitis C	6(23.1)	8(24.2)	
Alcoholism/others	4(15.4)	2(6.1)	
Performance status			0.648
ECOG = 0	6(23.1)	6(18.2)	
ECOG = 1	18(69.2)	22(66.7)	
ECOG = 2	2(7.7)	5(15.2)	
Extrahepatic metastases	2 (7.7%)	4 (12.1%)	0.580
Albumin (g/L)	3.44 ± 0.48	3.52 ± 0.52	0.838
Bilirubin (μmol/L)	0.75 ± 0.39	1.27 ± 2.33	0.078
Albumin-bilirubin gradient index			0.950
1	4 (15.4%)	6 (18.2%)	
2	21 (80.8%)	26 (78.8%)	
3	1 (3.8%)	1 (3.0%)	
AFP (ng/mL)			0.683
≥20	16(61.5)	22(66.7)	
<20	10(38.5)	11(33.3)	
Serum creatinine (mg/dL)	0.88 ± 0.24	0.99 ± 0.81	0.506
Asparate aminotransferase (U/L)	47.39 ± 18.63	83.42 ± 91.42	0.053
Alanine aminotransaminase (U/L)	27.69 ± 15.98	45.03 ± 23.55	0.002*
Prothrombin time (second)	11.41 ± 2.02	11.12 ± 0.83	0.457
International normalized ratio	1.08 ± 0.21	1.06 ± 0.09	0.624
Platelet count (10^3/mL)	179.85 ± 101.32	191.18 ± 121.71	0.704
Ascites			0.113
Present	14(53.8)	11(33.3)	
Absent	12(46.2)	22(66.7)	
Child-Pugh class			0.179
A	12(46.2)	21(63.6)	
B	14(53.8)	12(36.4)	
Tumor burden			0.211
50%-70%	12(46.2)	10(69.7)	
<50%	14(53.8)	23(30.3)	
Median dosage of sorafenib (mg/day)	700.00 ± 185.16	723.08 ± 150.49	1.000
Treatment duration of sorafenib (day)	382.50 ± 513.90	259.89 ± 304.89	0.989

AFP = alpha-fetoprotein; ECOG = Eastern Cooperative Oncology Group; HAVS = hepatic arteriovenous shunt; HCC = hepatocellular carcinoma.
*p < 0.05.

Table 2

Pre-TACE imaging characteristics

Imaging characteristics	Advanced HCC without HAVS (n = 26)	Advanced HCC with HAVS (n = 33)	p
Tumor size			0.438
≤5 cm	6 (23.1)	5 (15.2)	
>5 cm	20 (76.9)	28 (84.8)	
Tumor involvement			0.211
Unilobar	14 (53.8)	23 (69.7)	
Bilobar	12 (46.2)	10 (30.3)	
Morphology			0.274
Nodule/mass	22 (84.6)	24 (72.7)	
Infiltrative appearance	4 (15.4)	9 (27.3)	
Presence of capsule			0.522
Present	12 (46.2)	18 (54.5)	
Absent	14 (53.8)	15 (45.5)	
Arterial phase hyperenhancement			0.452
Homogeneous	2 (7.7)	1 (3.0)	
Inhomogeneous	24 (92.3)	30 (97.0)	
Ancillary features			
Mosaic	6 (23.1)	8 (25.8)	0.812
Nodule-in-nodule sign	14 (53.8)	18 (56.3)	0.855
Intratumoral hemorrhage	2 (7.7)	6 (18.2)	0.243
Portal vein tumor thrombosis			0.002*
Low grade	24 (92.3)	19 (57.6)	
High grade	2 (7.7)	14 (42.4)	

HAVS = hepatic arteriovenous shunt; HCC = hepatocellular carcinoma; TACE = transarterial chemoembolization.
*p < 0.05.

Table 3

Locoregional tumor response and survival for the two groups

Parameters	Advanced HCC without HAVS (n = 26)	Advanced HCC with HAVS (n = 33)	*p*
Volume reduction (%)			0.492
≥30%	19 (69.2)	20 (60.6)	
<30%	8 (30.8)	13 (39.4)	
Presence of new lesions			0.358
Presence	8 (30.8)	14 (42.4)	
Absent	18 (69.2)	19 (57.6)	
Tumor response (n, %)			0.030
Complete response (CR)	6 (23.1)	0 (0.0)	
Partial response (PR)	12 (46.2)	20 (60.6)	
Stable disease (SD)	6 (23.1)	9 (27.3)	
Progressive disease (PD)	2 (7.7)	4 (12.1)	
Objective response rate (CR + PR)	18 (69.2)	20 (60.6)	0.492
Disease control rate (CR + PR + SD)	24 (92.3)	29 (87.9)	0.685
Time to progression (months, median ± SD)	4.23 ± 0.65	2.33 ± 0.33	0.235
Overall survival (months, median ± SD)	12.97 ± 2.80	12.77 ± 3.86	0.910

HAVS = hepatic arteriovenous shunt; HCC = hepatocellular carcinoma.

The group without HAVS demonstrated a significantly lower AER_{PVTT} than those with HAVS (0.33 ± 0.25 vs 1.15 ± 0.57 HU, $p < 0.001$). After TACE, the group without HAVS had a lower AER_{Tumor} (0.25 ± 0.23 vs 0.55 ± 0.43 HU, $p = 0.005$). There was no significant difference in the AER_{PVTT} between the two groups after TACE ($p = 0.262$). Changes in AER before and after TACE for both tumors and PVTT were also calculated, and the drop in AER_{Tumor} was greater in the group without HAVS than in the group with HAVS (–0.66 ± 0.55 vs –0.37 ± 0.43 HU, $p = 0.028$) (as shown in Figs. 2A–D and 3A–D). In contrast, the group with HAVS had a significant drop in the AER_{PVTT} (–0.69 ± 0.78 vs –0.03 ± 0.31 HU in the group without HAVS, $p < 0.001$).

Table 4

Pre-TACE and post-TACE arterial enhancement ratio of tumor and portal vein tumor thrombosis

CT measurements	Advanced HCC without HAVS (n = 26)	Advanced HCC with HAVS (n = 33)	*p*
Pre-TACE			
Arterial enhancement ratio			
Tumor attenuation	0.90 ± 0.46	0.92 ± 0.44	0.874
PVTT attenuation	0.33 ± 0.25	1.15 ± 0.57	<0.001*
Post-TACE			
Arterial enhancement ratio			
Tumor attenuation	0.25 ± 0.23	0.55 ± 0.43	0.005*
PVTT attenuation	0.30 ± 0.19	0.46 ± 0.45	0.262
Change of arterial enhancement ratio			
Tumor attenuation	–0.66 ± 0.55	–0.37 ± 0.43	0.028*
PVTT attenuation	–0.03 ± 0.31	–0.69 ± 0.78	<0.001*

HAVS = hepatic arteriovenous shunt; HCC = hepatocellular carcinoma; TACE = transarterial chemoembolization; PVTT = portal vein tumor thrombosis.
*$p < 0.05$.

3.4. Time-to-progression and OS

As shown in Table 3, the median TTP was longer in the group without HAVS than in the group with HAVS but showed no significant difference (4.23 ± 0.65 vs 2.33 ± 0.33 months, $p = 0.235$). The median OS was 12.97 ± 2.80 months for the group without HAVS and 12.77 ± 3.86 months for those with HAVS ($p = 0.910$). The Kaplan-Meier estimated survival curves are shown in Fig. 4.

The clinical, radiological, and laboratory parameters achieving significant differences between the two groups were enrolled in both univariate and multivariate analyses of prognostic factors for TTP (Table 5) and OS (Table 6). Objective response independently predicted longer TTP in both univariate and multivariate analyses. Regarding OS, both univariate and multivariate analyses revealed that a decrease in tumor AER > 20% was the only significant factor associated with better OS.

3.5. Safety of combination therapy

The overall post-TACE adverse events among the two groups are shown in Fig. 5. A total of 24 patients (40.7%) experienced transient grade 3/4 AST/ALT elevation (38.5% in the group without HAVS vs 42.4% in the group with HAVS), but there was no documented hepatic failure within 6 weeks after TACE. One patient in the group with HAVS had transient and self-limiting gastrointestinal bleeding. Two patients in the group without HAVS (7.7%) and one patient in the group with HAVS (3.0%) developed abscess/biloma formation that required percutaneous tube drainage. Regarding sorafenib-related adverse events, two patients without HAVS experienced hand-foot skin reaction; in patients with HAVS, there was one episode of hand-foot skin reaction and one episode of hair loss; there was no difference in the incidence between the two groups (7.7% in patients without HAVS and 6.6% in patients with HAVS; $p = 1.000$).

4. DISCUSSION

This study showed that with the combination therapy of sorafenib and DEB-TACE, the presence of HAVS did not affect the prognosis of advanced HCC patients with PVTT. The two groups had similar tumor responses after DEB-TACE (ORR: 69.2% in the group without HAVS vs 60.6% in the group with HAVS; DCR: 92.3% vs 87.9%), and there was no difference in TTP (4.23 ± 0.65 vs 2.33 ± 0.33 months, $p = 0.235$) or OS (12.97 ± 2.80 vs 12.77 ± 3.86 months, $p = 0.910$) between the two groups. With regard to safety, no difference in the occurrence of hepatic failure and TACE-related complications between the two groups was noted.

The existence of HAVS was conventionally considered a contraindication to TACE due to the concern of nontarget embolization of normal hepatic tissue via pathological shunts. To avoid this possible complication, several techniques have been utilized to embolize the shunt, including gelfoam, coil, and cyanoacrylate glue.[8,10,21,22] Recently, with the development of DEB-TACE, this new drug-delivering system has been applied in the treatment of HCC with arterioportal shunting[23] and is considered a feasible and safe management. In this study, we also chose DEB-TACE in the treatment of HCC with HAVS. Patients with HAVS had a significant drop in AER_{PVTT} after DEB-TACE, indicating successful shunt embolization, and this change was not demonstrated in patients without HAVS. However, this drop in AER_{PVTT} was not correlated with OS (as shown in Table 5). Notably, subgroup analysis showed that the grade of PVTT in this study did not correlate with OS, which conflicts with a previous study,[5] which concluded that the main PVTT had a negative impact on OS

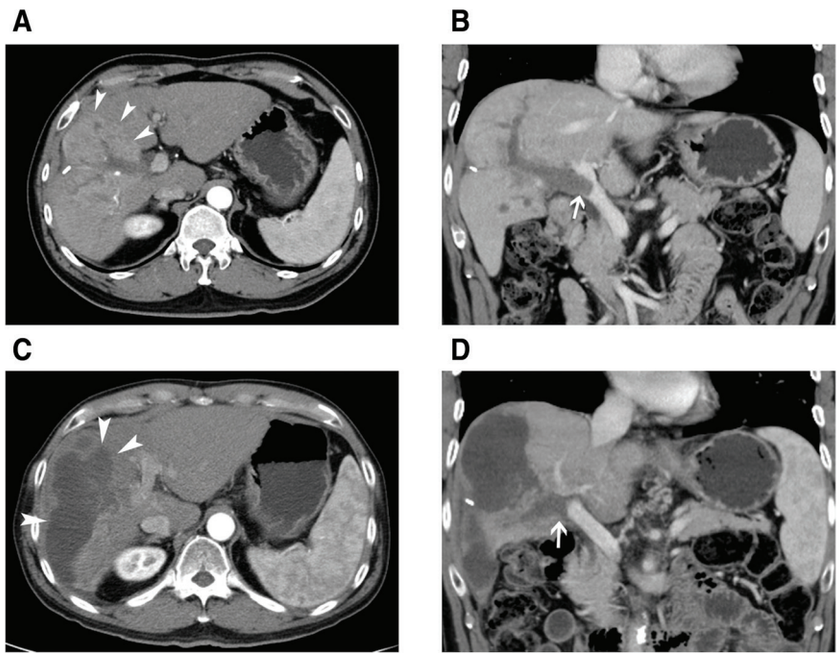

Fig. 2 Infiltrative HCCs with portal vein tumor thrombosis (PVTT) and arterioportal shunting (APS) in a 45-year-old man with HBV-related liver cirrhosis. A and B, The arterial phase of CT before DEB-TACE showed ill-defined infiltrative HCCs in the right lobe of liver (asterisk in A), with PVTT of main portal vein (arrow in A). The coronal view of portal venous phase revealed APS near the hepatic hilum (arrowheads in B). C, During TACE, the digital subtraction angiography of superior branch of right hepatic artery (arrowheads) revealed low-flow APS (arrow). After embolizing the APS with gelfoam sponges, DEB-TACE was performed with 30-60 μm Hepasphere. D, Three months after DEB-TACE, the arterial phase of MDCT demonstrated that most part of HCC in the right lobe (arrowheads) showed cystic necrosis, indicative of partial response (PR). Also note partial resolution of APS (arrow). DEB-TACE = drug-eluting bead transarterial chemoembolization; HCC = hepatocellular carcinoma.

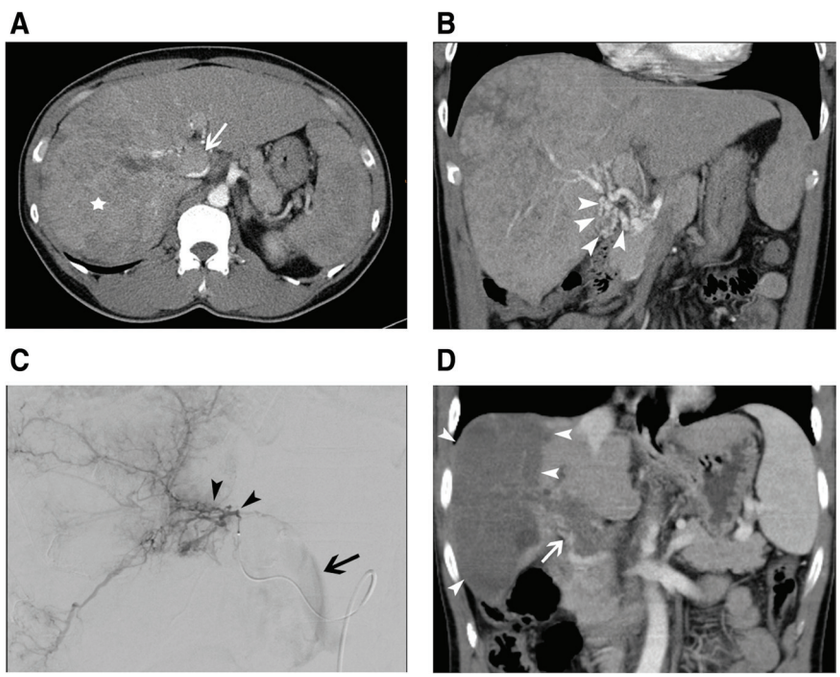

Fig. 3 Advance HCC with portal vein tumor thrombosis (PVTT) in a 52-year-old man with HBV-related liver cirrhosis. A and B, The arterial phase of CT before DEB-TACE showed a HCC in the right lobe of liver (arrowheads in A). The coronal view of portal venous phase revealed PVTT of right portal vein (arrow in B). C and D, Three months after DEB-TACE with 30-60 μm Hepasphere, the arterial phase of MDCT demonstrated that most part of HCC in the right lobe (arrowheads in C) showed cystic necrosis, indicative of partial response (PR). Also note partial resolution of PVTT in the right portal vein (arrow). DEB-TACE = drug-eluting bead transarterial chemoembolization; HCC = hepatocellular carcinoma.

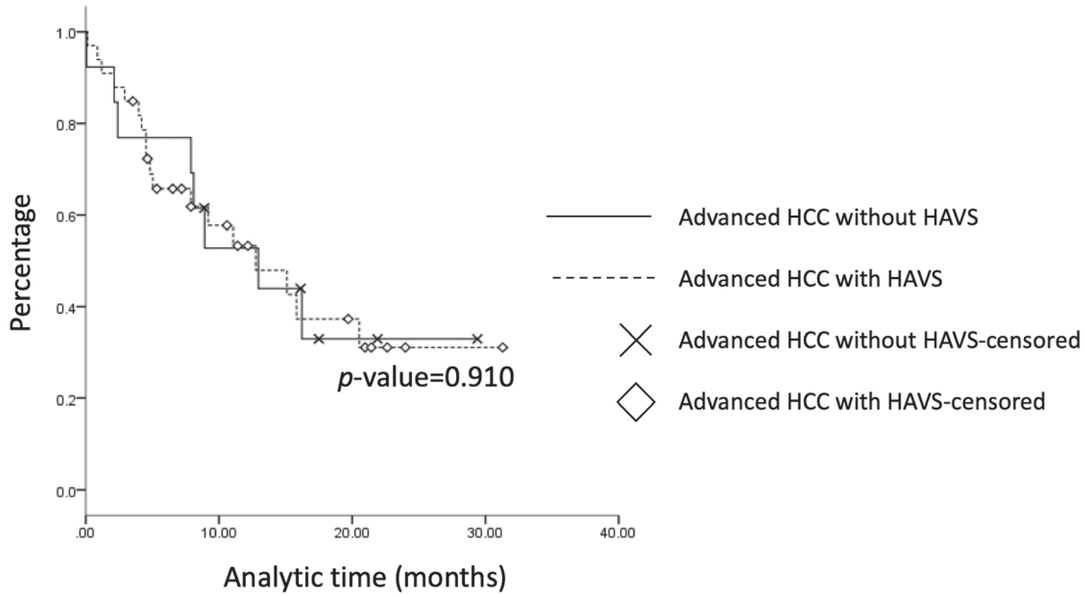

Fig. 4 Kaplan–Meier curve of time-to-progression (A) and overall survival (B) according to the presence of hepatic arteriovenous shunt (HAVS).

in patients treated with c-TACE and sorafenib. This discordance may be caused by different TACE approaches or embolizing agent selection for HAVS. Further head-to-head trials are warranted to confirm the treatment benefit of the main PVTT between c-TACE and DEB-TACE.

Previously, the presence of HAVS was considered a poor prognostic factor for HCC patients because it increases the risk of cirrhosis-related complications[24,25] and may cause the spread and metastasis of HCC.[12] Furthermore, HAVS will increase the difficulty of performing TACE in these patients, causing insufficient treatment. In this study, no prognostic difference was noted between the patients with HAVS (median OS: 12.77 ± 3.86 months) and those without HAVS (median OS: 12.97 ± 2.80 months). This can be explained by the fact that HAVS was embolized during TACE, which simultaneously lowered the risk of shunt-related complications and tumor spread. In theory, DEBs inevitably flow into the venous system with variable percentages if HAVS is present. This may reasonably explain why HCC patients without HAVS would have a better chance of complete embolization of the tumor blood supply, resulting in a greater decline in AER_{Tumor} and better OS than those with HAVS. However, there is no consensus regarding AER_{Tumor} and AER_{PVTT}. In this study, two different criteria were used to define the cutoff values because there is essentially a difference for HCC parenchymal tumors or portal vein lesions.[26,27] Similar to the diameter measurement criteria, we defined the cutoff value of AER_{Tumor} as 20% because we thought if the patient was responsive to combination therapy (remained at least stable condition), the lesion could be measured in one dimension (by mRECIST criteria). The cutoff value of AER_{PVTT} is 50% because we thought the portal vein lesion should be measured in two dimensions (which is by EASL criteria).

In HCC patients with PVTT, safety is a leading concern when performing TACE due to an increased risk of hepatic failure; compared with cTACE, DEB-TACE showed less liver toxicity[13] and may be a better option in these patients. Regarding

Table 5

Independent prognostic factors affecting time-to-progression as determined by univariate and multivariate analysis

		Univariate analysis			Multivariate analysis		
Variables	**Total**	**Hazard ratio**	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***
Pre-TACE							
HAVS	33	1.591	0.922-2.746	0.096			
Multiple tumors	38	1.086	0.622-1.896	0.7731			
High-grade PVTT	16	0.695	0.362-1.331	0.2722			
Extra-hepatic metastasis	6	1.381	0.580-3.286	0.466			
Albumin-bilirubin gradient index ≥2	49	0.889	0.444-1.780	0.739			
HAP score C-D	37	0.974	0.563-1.686	0.925			
Post-TACE							
>20% decrease in AER_{Tumor}	35	0.550	0.311-0.973	0.040	0.620	0.320-1.202	0.157
>50% decrease in AER_{PVTT}	8	1.626	0.724-3.654	0.239			
Objective response	38	0.331	0.184-0.597	<0.001*	0.340	0.154-0.751	0.008*
Disease control	53	0.411	0.172-0.987	0.047*	0.521	0.167-1.626	0.261
Adverse events of TKI	4	0.509	0.170-1.526	0.2279			

AER = arterial enhancement ratio; HAP = hepatoma arterial-embolization prognostic; HAVS = hepatic arteriovenous shunt; PVTT = portal vein tumor thrombosis; TKI = tyrosine kinase inhibitor.
*$p < 0.05$.

Table 6

Independent prognostic factors affecting overall survival as determined by univariate and multivariate analysis

		Univariate analysis			Multivariate analysis		
Variables	**Total**	**Hazard ratio**	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***
Pre-TACE							
HAVS	33	0.960	0.483-1.907	0.907			
Multiple tumors	38	0.841	0.413-1.713	0.633			
High-grade PVTT	16	0.779	0.338-1.780	0.559			
Extra-hepatic metastasis	6	1.204	0.361-4.018	0.762			
Albumin-bilirubin gradient index ≥2	49	1.704	0.598-4.853	0.318			
HAP score C-D	37	1.475	0.700-3.106	0.307			
Post-TACE							
>20% decrease in AER_{Tumor}	35	0.346	0.173-0.692	0.003	0.406	0.180-0.918	0.030
>50% decrease in AER_{PVTT}	8	1.105	0.386-3.157	0.8529			
Objective response	38	0.455	0.229-0.906	0.025	0.467	0.182-1.198	0.1134
Disease control	53	1.852	0.442-7.757	0.399			
Adverse events of TKI	4	0.000	---	0.9464			

AER = arterial enhancement ratio; HAP = hepatoma arterial-embolization prognostic; HAVS = hepatic arteriovenous shunt; PVTT = portal vein tumor thrombosis; TKI = tyrosine kinase inhibitor.

the presence of HAVS, this vascular anomaly may cause nontarget embolization of normal liver parenchyma and pulmonary tissues[28]; with the improvement of the TACE technique, this concern can be eliminated with the embolization of shunts before delivering DEBs. In this study, the most common adverse event after combination therapy of TACE and sorafenib within 1 month was transient elevation of liver enzymes, but none of these patients developed hepatic failure. There was no difference in grade 3-4 liver damage between the patients without HAVS and those with HAVS. Among this study, only one patient (3.0%) in the group with HAVS and two patients (7.7%) in the group without HAVS met the definition of major complications, in which tube drainage was indicated for liver abscesses or bilomas formation. In other words, performing DEB-TACE in HCC patients with HAVS is a safe management.

Sorafenib was recommended as the standard treatment for patients with advanced HCC[29,30] more than one decade ago, and prior data showed significantly improved survival in the sorafenib monotherapy group compared to the placebo group (6.5 vs 4.2 months). The TACTICS trial (only 12% HCC patients with PVTT)[31] is the first positive randomized prospective study of TACE-sorafenib therapy using a newly established TACE-specific endpoint, with prolonged median PFS (25.2 months vs 13.5 months) and 2-year longer survival (82.7% vs 64.6%) than TACE alone. Furthermore, TACE-sorafenib therapy to treat HCC with PVTT in patients with preserved liver function (Child-Pughs score < 7) is clinically feasible and safe. Similar to a recent controlled study,[5] we found that DEB TACE-sorafenib therapy in our study had a survival benefit (12.77 months) and TTP (2.33 months) compared to prior published data in the HCC with PVTT group in the first- or lower-order portal vein branches. We also noticed that adverse effects were more frequent in our study with DEB TACE-sorafenib therapy.

There are some limitations in this nonrandomized, prospective study. First, this analysis was conducted in a single institution with a relatively small patient number. Second, treatment response by cutoff values for AER_{Tumor} and AER_{PVTT} were likely underrepresented, so correlations to long-term outcomes are hypothesis-generating. Further analyses on prospective multicenter clinical trials with these criteria are necessary to validate the cutoff values. Third, classifying and measuring CT findings before and after DEB-TACE are intrinsically subjective, and interobserver agreement is needed in future investigations. Finally, adequate HAVS management and embolization are operator-dependent and lack a standardized protocol, which may cause bias to therapeutic efficacy.

In conclusion, this study showed that combination therapy of sorafenib and DEB-TACE had equivalent safety and efficacy

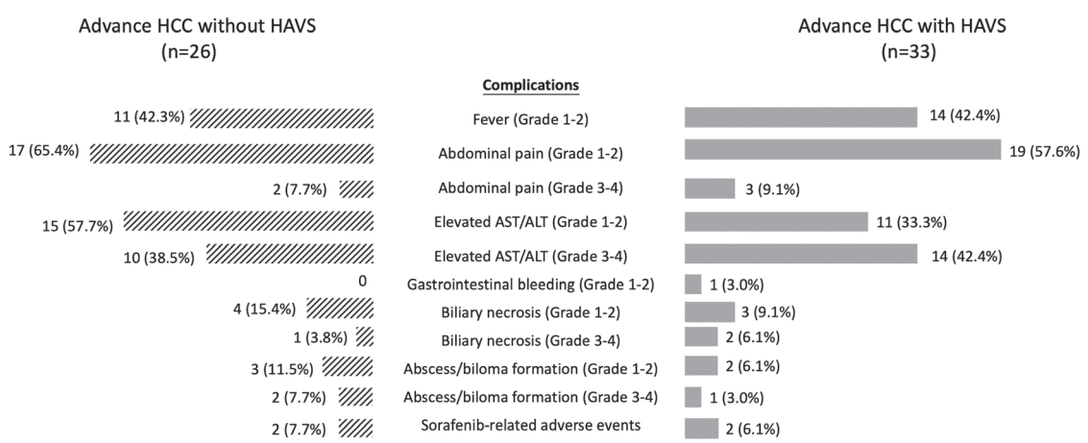

Fig. 5 Complications occurred within 6 weeks after DEB-TACE. HAVS: hepatic arteriovenous shunt. DEB-TACE = drug-eluting bead transarterial chemoembolization.

in advanced HCC patients with HAVS compared to those without HAVS, indicating that DEB-TACE is an optional and effective treatment in these patients. Among patients with HAVS, the decrease in AER_{Tumor} at the first follow-up at 1 month.

ACKNOWLEDGMENTS

This study was supported by a study project of the Ministry of Science of Technology (MOST 109-2314-B-016-012).

We thank the Cancer Registry Group of Tri-Service General Hospital for the clinical data support.

REFERENCES

1. Okuda K, Musha H, Yamasaki T, Jinnouchi S, Nagasaki Y, Kubo Y, et al. Angiographic demonstration of intrahepatic arterio-portal anastomoses in hepatocellular carcinoma. *Radiology* 1977;**122**:53–8.
2. Nonami T, Yokoyama I, Iwatsuki S, Starzl TE. The incidence of portal vein thrombosis at liver transplantation. *Hepatology* 1992;**16**:1195–8.
3. Vogl TJ, Nour-Eldin NE, Emad-Eldin S, Naguib NN, Trojan J, Ackermann H, et al. Portal vein thrombosis and arterioportal shunts: effects on tumor response after chemoembolization of hepatocellular carcinoma. *World J Gastroenterol* 2011;**17**:1267–75.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;**69**:182–236.
5. Zhu K, Chen J, Lai L, Meng X, Zhou B, Huang W, et al. Hepatocellular carcinoma with portal vein tumor thrombus: treatment with transarterial chemoembolization combined with sorafenib–a retrospective controlled study. *Radiology* 2014;**272**:284–93.
6. Ngan H. Interventional radiology for hepatocellular carcinoma. *Dig Surg* 1995;**12**:65–72
7. Liu QS, Mei QL, Li YH. Polyvinyl alcohol terminal chemoembolization for hepatocellular carcinoma with hepatic arteriovenous shunts: safety, efficacy, and prognostic factors. *Eur J Radiol* 2017;**89**:277–83.
8. Shi HB, Yang ZQ, Liu S, Zhou WZ, Zhou CG, Zhao LB, et al. Transarterial embolization with cyanoacrylate for severe arterioportal shunt complicated by hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2013;**36**:412–21.
9. Kim YJ, Lee HG, Park JM, Lim YS, Chung MH, Sung MS, et al. Polyvinyl alcohol embolization adjuvant to oily chemoembolization in advanced hepatocellular carcinoma with arterioportal shunts. *Korean J Radiol* 2007;**8**:311–9.
10. Furuse J, Iwasaki M, Yoshino M, Konishi M, Kawano N, Kinoshita T, et al. Hepatocellular carcinoma with portal vein tumor thrombus: embolization of arterioportal shunts. *Radiology* 1997;**204**:787–90.
11. Zhou WZ, Shi HB, Liu S, Yang ZQ, Zhou CG, Xia JG, et al. Arterioportal shunts in patients with hepatocellular carcinoma treated using ethanol-soaked gelatin sponge: therapeutic effects and prognostic factors. *J Vasc Interv Radiol* 2015;**26**:223–30.
12. Murata S, Tajima H, Nakazawa K, Onozawa S, Kumita S, Nomura K. Initial experience of transcatheter arterial chemoembolization during portal vein occlusion for unresectable hepatocellular carcinoma with marked arterioportal shunts. *Eur Radiol* 2009;**19**:2016–23.
13. Nouri YM, Kim JH, Yoon HK, Ko HK, Shin JH, Gwon DI. Update on transarterial chemoembolization with drug-eluting microspheres for hepatocellular carcinoma. *Korean J Radiol* 2019;**20**:34–49.
14. Shi Q, Chen D, Zhou C, Liu J, Huang S, Yang C, et al. Drug-eluting beads versus lipiodol transarterial chemoembolization for the treatment of hypovascular hepatocellular carcinoma: a single-center retrospective study. *Cancer Manag Res* 2020;**12**:5461–8.
15. Chiu SH, Chang PY, Shih YL, Huang WY, Ko KH, Chang WC, et al. Efficacy and safety of supplemental transarterial chemoembolization through extrahepatic collateral arteries with drug-eluting beads: treatment for unresectable hepatocellular carcinoma. *Drug Des Devel Ther* 2020;**14**:5029–41.
16. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;**68**:723–50.
17. Chernyak V, Fowler KJ, Kamaya A, Kielar AZ, Elsayes KM, Bashir MR, et al. Liver Imaging Reporting and Data System (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. *Radiology* 2018;**289**:816–30.
18. Patchett N, Furlan A, Marsh JW. Decrease in tumor enhancement on contrast-enhanced CT is associated with improved survival in patients with hepatocellular carcinoma treated with Sorafenib. *Jpn J Clin Oncol* 2016;**46**:839–44.
19. Salvaggio G, Furlan A, Agnello F, Cabibbo G, Marin D, Giannitrapani L, et al. Hepatocellular carcinoma enhancement on contrast-enhanced CT and MR imaging: response assessment after treatment with sorafenib: preliminary results. *Radiol Med* 2014;**119**:215–21.
20. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;**30**:52–60.
21. Tarazov PG. Intrahepatic arterioportal fistulae: role of transcatheter embolization. *Cardiovasc Intervent Radiol* 1993;**16**:368–73.
22. Clark RA, Frey RT, Colley DP, Eiseman WR. Transcatheter embolization of hepatic arteriovenous fistulas for control of hemobilia. *Gastrointest Radiol* 1981;**6**:353–6.
23. Xiao YD, Ma C, Zhang ZS, Liu J. Safety and efficacy assessment of transarterial chemoembolization using drug-eluting beads in patients with hepatocellular carcinoma and arterioportal shunt: a single-center experience. *Cancer Manag Res* 2019;**11**:1551–7.
24. Velázquez RF, Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorríos NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003;**37**:520–7.
25. Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol* 2016;**64**:1090–8.
26. Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. *J Hepatol* 2020;**72**:288–306.
27. Yaghmai V, Besa C, Kim E, Gatlin JL, Siddiqui NA, Taouli B. Imaging assessment of hepatocellular carcinoma response to locoregional and systemic therapy. *AJR Am J Roentgenol* 2013;**201**:80–96.
28. Ziessman HA, Thrall JH, Yang PJ, Walker SC, Cozzi EA, Niederhuber JE, et al. Hepatic arterial perfusion scintigraphy with Tc-99m-MAA. Use of a totally implanted drug delivery system. *Radiology* 1984;**152**:167–72.
29. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378–90.
30. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;**10**:25–34.
31. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020;**69**:1492–501.