Liver Cancer

Research Article

Liver Cancer 2022;11:440–450
DOI: 10.1159/000525500

Received: February 3, 2022
Accepted: May 31, 2022
Published online: June 15, 2022

Conventional or Drug-Eluting Beads? Randomized Controlled Study of Chemoembolization for Hepatocellular Carcinoma: JIVROSG-1302

Masafumi Ikeda[a] Yasuaki Arai[b] Yoshitaka Inaba[c] Toshihiro Tanaka[d] Shunsuke Sugawara[e] Yoshihisa Kodama[f] Takeshi Aramaki[g] Hiroshi Anai[h] Shinichi Morita[i] Yoshinori Tsukahara[j] Hiroshi Seki[k] Mikio Sato[l] Kenya Kamimura[m] Kimei Azama[n] Masakatsu Tsurusaki[o] Eiji Sugihara[p] Masaya Miyazaki[q] Tatsushi Kobayashi[r] Miyuki Sone[e]

[a]Department of Hepatobiliary & Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [b]Executive Advisor to the President, National Cancer Center, Tokyo, Japan; [c]Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, Nagoya, Japan; [d]Department of Radiology, IVR Center, Nara Medical University, Kashihara, Japan; [e]Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan; [f]Department of Radiology, Teine Keijinkai Hospital, Sapporo, Japan; [g]Division of Interventional Radiology, Shizuoka Cancer Center, Shizuoka, Japan; [h]Department of Radiology, Nara City Hospital, Nara, Japan; [i]Department of Gastroenterology and Hepatology, Uonuma Institute of Community Medicine, Niigata University Hospital, Minamiuonuma, Japan; [j]Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan; [k]Department of Diagnostic Radiology, Niigata Cancer Center Hospital, Niigata, Japan; [l]Department of Gastroenterology and Hepatology, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan; [m]Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan; [n]Department of Radiology, Ryukyu University Hospital, Nishihara, Japan; [o]Department of Radiology, Kindai University Faculty of Medicine, Osaka-sayama, Japan; [p]Department of Diagnostic Imaging, Osaka General Medical Center, Osaka, Japan; [q]Department of Applied Medical Imaging, Gunma University Graduate School of Medicine, Maebashi, Japan; [r]Department of Diagnostic Radiology, National Cancer Center Hospital East, Kashiwa, Japan

Keywords
Hepatocellular carcinoma · Transarterial chemoembolization · Drug-eluting beads · Ethiodized oil · Epirubicin

Abstract

Introduction: With the advent of effective systemic therapy, transarterial chemoembolization (TACE) is established as a highly effective locoregional treatment modality for carefully selected patients with hepatocellular carcinoma (HCC). This randomized controlled trial was conducted to clarify whether selective TACE with drug-eluting beads (DEB-TACE) loaded with epirubicin or selective conventional TACE (cTACE) with epirubicin-ethiodized oil might be more effective for obtaining complete response(CR) in patients with HCC. ***Methods:*** Between March 2016 and May 2019, Child-Pugh class A or B patients with unresectable HCC who were scheduled to receive selective TACE were randomly assigned at a 1:1 ratio to the DEB-TACE arm or the cTACE arm. The primary endpoint was the CR rate at 3 months, as evaluated according to the modified Response Evaluation Criteria in Sol-

Karger@karger.com
www.karger.com/lic

Correspondence to:
Masafumi Ikeda, masikeda@east.ncc.go.jp

id Tumors by an independent review committee, and the secondary endpoints were the CR rate at 1 month and incidences of adverse events. ***Results:*** A total of 200 patients (DEB-TACE, 99 patients; cTACE, 101 patients) were enrolled in the study. The CR rates at 3 months and 1 month were significantly higher in the cTACE arm (75.2%, 84.2%) as compared with the DEB-TACE arm (27.6%, 35.7%). However, the frequencies of adverse events of any grade, including pyrexia (DEB-TACE vs. cTACE, 19.4% vs. 45.5%, $p = 0.0001$), fatigue (5.1% vs. 15.8%, $p = 0.0194$), malaise (11.1% vs. 25.7%, $p = 0.0103$), appetite loss (12.1% vs. 28.7%, $p = 0.0048$), abdominal pain (12.1% vs. 23.8%, $p = 0.0423$), increased serum bilirubin (22.2% vs. 48.5%, $p = 0.0002$), hypoalbuminemia (43.4% vs. 60.3%, $p = 0.0154$), increased serum aspartate aminotransferase (35.7% vs. 81.2%, $p < 0.0001$), and increased serum alanine aminotransferase (35.7% vs. 77.2%, $p < 0.0001$), were also significantly higher in the cTACE arm than in the DEB-TACE arm. ***Conclusions:*** Selective cTACE appeared to have higher CR rates for local tumor control as compared to selective DEB-TACE for HCC. However, the frequency of postembolization syndrome was also significantly higher in the cTACE group than in the DEB-TACE group. Thus, to achieve CR, cTACE may be selected over DEB-TACE in patients who can be expected to tolerate postembolization syndrome.

Introduction

Transarterial chemoembolization (TACE) is established worldwide as the standard treatment modality for patients with unresectable hepatocellular carcinoma (HCC) [1], based on the results of several randomized controlled trials and meta-analyses [2, 3]. There are two types of TACE, conventional TACE (cTACE) and drug-eluting TACE. cTACE involves administration of an anticancer agent emulsified in ethiodized oil, followed by embolization of the tumor-feeding artery with gelatin sponge particles, and is widely used as a practical standard treatment in Asian countries [4, 5]. TACE with drug-eluting beads (DEB-TACE) involves administration of spherical drug-eluting microspheres loaded with an anticancer agent.

Some randomized controlled trials comparing DEB-TACE with cTACE [6–9] have been reported. Lammer et al. [6], who conducted the PRECISION V trial, reported the absence of any significant difference in the response rate at 6 months, as the primary endpoint, between the DEB-TACE and cTACE arms. In subgroup analyses, DEB-TACE was associated with a higher response rate as compared with cTACE in patients with Child-Pugh class B, an Eastern Cooperative Clinical Oncology Group Performance Status of 1, bilobar disease, and recurrent disease. Also, the incidence of worsening of the liver function after TACE was significantly lower in the DEB-TACE group than in the cTACE group. According to the PRECISION Italy trial conducted by Golfieri et al. [7], there was no significant difference in either the overall survival or progression-free survival between patient groups treated by DEB-TACE and cTACE, although the incidence of pain post-TACE was lower in the DEB-TACE group than in the cTACE group. Furthermore, the complete response (CR) rates at 1 month, 3 months, 6 months, 9 months, and 12 months after TACE were almost equivalent between patient groups treated by DEB-TACE and cTACE. Many retrospective comparative studies and meta-analyses [10–14] have reported similar results to those of the aforementioned trials [6–9]. Thus, DEB-TACE and cTACE are generally considered to have equivalent efficacy, although the incidence of postembolization syndrome clearly appears to be lower after DEB-TACE than after cTACE.

HCC patients with a limited number and size of the nodules are often treated by TACE, with selective catheterization of the segmental or subsegmental hepatic arteries feeding the HCC, and favorable CR rates have been reported [15–17]. Matsui et al. [15] reported a CR rate of 67% of HCC tumors ≤4 cm in diameter treated by selective cTACE. Golfieri et al. [17] also reported that complete necrosis was achieved in 53.8% of HCC tumors treated by selective cTACE; they identified presence of a single nodule and selective TACE as predictors of complete tumor necrosis. Thus, small-sized HCC nodules appear to show higher CR rates to selective TACE. The guideline of the European Association for the Study of the Liver (EASL) [18] and the ESMO clinical practice guidelines [19] recommend that TACE should be carried out in a selective manner.

With the advent of effective systemic chemotherapeutic agents/regimens [20], such as atezolizumab plus bevacizumab [21] and lenvatinib [22], TACE is expected as a treatment modality for locoregional control and radical cure because systemic therapies have been shown to elicit high tumor response (atezolizumab plus bevacizumab, 27.3%, according to the Response Evaluation Criteria in Solid Tumors [RECIST]; lenvatinib, 40.6%, according to the modified RECIST) and can play a role as palliative therapy. The guideline of the EASL mentions that according to meta-analyses, the objective response as measured

by the modified RECIST is predictive of the overall survival in patients receiving locoregional therapies [18]. It also mentions that patients who show CR to the initial TACE exhibit significantly longer overall survival rates, suggesting the importance of achieving CR following even the initial TACE procedure [18, 23]. The Asia-Pacific Primary Liver Cancer Expert Consensus Statement on the treatment strategy for patients with intermediate-stage HCC [24] states that the tumor response according to the modified RECIST is predictive of the overall survival in patients receiving TACE; in particular, CR to the initial TACE, could be predictive of a longer survival. Although a number of reports have suggested that selective TACE is more effective to obtain CR than nonselective TACE, it still remains to be clarified which of the two techniques, selective DEB-TACE or selective cTACE, might be more effective to achieve CR. Therefore, we conducted this randomized controlled trial to compare the CR rates to selective DEB-TACE and selective cTACE in patients with unresectable HCC.

Patients and Methods

Study Design

This study, the JIVROSG-1302 PRESIDENT study, was a Japanese multicenter, unblinded, prospective randomized controlled trial of selective DEB-TACE versus selective cTACE with epirubicin in patients with advanced HCC, focused on the local tumor control rate. The aim of this study was to determine whether selective cTACE or selective DEB-TACE might be superior to achieve CR. The primary endpoint was the CR rate at 3 months, assessed according to the modified RECIST criteria by an independent review committee (IRC) [25]. The secondary endpoints were the CR rate at 1 month, assessed according to the modified RECIST criteria by the IRC, and the frequency/severity of adverse events. The study protocol was approved by the Institutional Review Boards of the National Cancer Center and the participating centers, and the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. This trial is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), with the identification number UMIN 000021250 (https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000024439).

Patient Eligibility

The main patient inclusion criteria were (1) histologically or clinically diagnosed HCC; (2) not eligible for surgical resection, liver transplantation, or local ablation therapy; (3) hypervascular tumor(s) showing early phase enhancement on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI); (4) suitable candidate for selective TACE; (5) no previous history of treatment of the HCC nodules for which TACE is planned; (6) nodule(s) for which TACE is planned amenable to measurement on CT/MRI; i.e., minimum diameter, 10 mm; (7) maximum diameter of 5 cm or smaller; (8) Eastern Cooperative Clinical Oncology Group Performance Status 0–1; (9) Child-Pugh class A or B; (10) age 20 years or over; (11) written informed consent available. There was no limitation placed on the number of targeted HCC nodules in each patient. In this trial, patients who had a prior history of TACE were also eligible, provided the target nodules were not the ones that had been treated by the prior TACE.

The main exclusion criteria were (1) presence of tumor thrombosis in the portal vein; (2) presence of extrahepatic metastasis; (3) rupture of the HCC nodule(s) for which TACE was planned; (4) clinically significant refractory ascites or pleural effusion. The full set of eligibility criteria is provided in the trial protocol, available in online Supplement 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000525500).

Treatments

The enrolled patients were randomly assigned at a ratio of 1:1 at enrollment to the selective DEB-TACE or selective cTACE arm. Randomization was performed centrally using the minimization method. The stratification factors for randomization were the maximum tumor diameter (≤3 cm/>3 cm), number of tumors (single/multiple), and institution.

Selective DEB-TACE was performed using drug-eluting beads (DC bead®: Eisai, Japan) loaded with epirubicin [26]. Before the embolization, each vial of DC bead® was loaded with 75 mg of epirubicin (Farmorubicin®: Pfizer, Japan, or Kyowa Hakko, Japan) mixed with nonionic contrast medium. Use of 100- to 300-μm particles is recommended for the first administration, and a maximum of two vials was permitted per TACE session. If additional embolization was needed, bland embolization, without epirubicin, was permitted. Selective cTACE was performed by administration of epirubicin emulsified in ethiodized oil (Lipiodol®: Guerbet, Japan), followed by that of porous gelatin particles (Gelpart®: Nippon Kayaku, Japan) [5]. The method used for preparing the emulsion of epirubicin and ethiodized oil was left to the discretion of each participant institution but generally adjusted to 10 mg of epirubicin dissolved in 1 mL nonionic contrast to 1–2 mL of ethiodized oil. The maximum dose of epirubicin was set at 150 mg per session. In both the treatment arms, a microcatheter was inserted into a segmental or more peripheral branch of the tumor-feeding artery, and the patient received the assigned type of TACE. The protocol demanded that the assigned TACE treatment be performed via a segmental or subsegmental branch of the tumor-feeding artery and that the treatment be ended when tumor enhancement in the target area could no longer be visualized. Each treatment was performed with reference to the technical recommendations for DEB-TACE [26] and cTACE [5]. The protocol treatment was allowed twice within 1 month (Split TACE) if the treatment could not be completed in one session. If contrast-enhanced CT/MRI at 1 month after TACE revealed CR, additional evaluation by contrast-enhanced CT/MRI was carried out at 3 months after TACE without any additional anticancer treatment in the intervening 2-month period.

Assessments

Evaluation of the tumor response was performed by contrast-enhanced CT or MRI at 1 and 3 months after TACE, in accordance with the modified RECIST [25]. Evaluation by contrast-enhanced CT is difficult in patients treated by cTACE using ethiodized oil because ethiodized oil could cause halation of the treated lesion. Therefore, the responses were evaluated by a central IRC, compris-

ing 6 radiologists. Adverse events were assessed in accordance with the Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analysis

The primary endpoint was the CR rate at 3 months as assessed in accordance with the modified RECIST by the IRC. In regard to the statistical assumption, the CR rate at 3 months was assumed to be 45% in the cTACE arm, based on a prospective trial of cTACE conducted by our group [4], and 25% in the DEB-TACE arm, based on the results of the PRECISION V trial [6]. The one-sided α-error and statistical power were set at 0.025 and 75%, respectively. The required sample size was calculated as 192 patients. Considering ineligible patients for the analysis, we set the target sample size at 100 patients per arm, that is, a total of 200 patients. The differences in the categorical data, including the frequency/severity of adverse events between the two arms, the odds ratios, and the 95% confidence interval (CI) of the treatment effects were estimated by Fisher's exact test. All reported p values are two-sided, and $p < 0.05$ was considered as being indicative of statistical significance. These analyses were conducted in the eligible patients, excluding those patients who could not receive the protocol treatment (full analysis set [FAS]). Subgroup analyses for primary endpoint were prespecified in the patient characteristics. Patient registration, random allocation, and data collection were managed by the EP-CRSU Data Center, Japan. All the data were fixed on March 25, 2020, and all the analyses of efficacy were performed based on the data of the FAS by the trial statistician, EPS cooperation, using SAS 9.4 and JMP Pro 11.

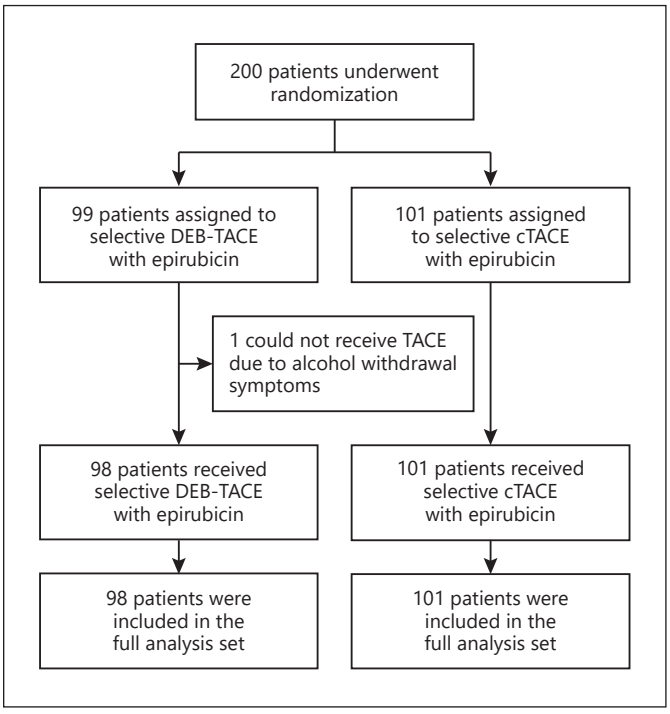

Fig. 1. Trial profile.

Results

Patient Characteristics

A total of 200 patients (DEB-TACE arm, 99 patients; cTACE arm, 101 patients) from 20 Japanese institutions were enrolled in this study between March 2016 and May 2019 (Fig. 1). One patient from the DEB-TACE arm, in whom TACE could not be performed because of alcohol withdrawal symptoms, was excluded from the FAS. Therefore, the study subjects included in the FAS were 98 patients of the DEB-TACE arm and 101 patients of the cTACE arm, that is, a total of 199 patients. During the TACE procedures, vascular invasion in a minor hepatic vein (Vv1) and minor portal vein (Vp1) was found in 1 patient of the DEB-TACE arm and 1 patient of the cTACE arm, respectively. Because these patients were judged as being eligible at enrollment, they were not excluded from this analysis. One patient of the cTACE arm did not undergo CT/MRI evaluation at 1 month, although the evaluation at 3 months indicated CR. This patient was treated as a "not evaluated" case according to the protocol. The characteristics of the patients in the FAS are shown in Table 1. The target nodule selected for TACE was single in 52 patients (53.1%) of the cTACE arm and 54 patients (53.5%) of the DEB-TACE arm. The maximum tumor diameter was less than 30 mm in 72 patients (73.5%) in the cTACE arm and 74.5 patients (74.3%) in the DEB-TACE arm. The patient characteristics were well-balanced between the two arms.

TACE Procedure

Selective TACE was performed using angiographic CT or cone beam CT and could be completed in all patients of both the treatment arms (Table 2). The success rate was 100% in both arms. Split TACE was performed in none of the patients of the DEB-TACE arm and 2 patients of the cTACE arm. The embolization was performed from the segmental branch in 13 patients and subsegmental branch in 85 patients of the DEB-TACE arm, and 4 and 97 patients, respectively, in the cTACE arm. The median dose of epirubicin was similar in both arms (DEB-TACE, 22.5 mg; cTACE, 25 mg). Seven patients (7.1%) in the DEB-TACE arm received additional bland embolization without epirubicin.

CR Rate

At the 1-month evaluation of the treatment response, 11 patients (1 patient of the cTACE arm and 10 patients of the DEB-TACE arm) were evaluated by MRI, and the

Table 1. Patient characteristics

Characteristic	DEB-TACE (*n* = 98)	cTACE (*n* = 101)
Median age, years [range]	74.5 [24–87]	73 [38–90]
Sex, *n* (%)		
Male	70 (71.4)	68 (67.3)
Female	28 (28.6)	33 (32.7)
ECOG-PS, *n* (%)		
0	88 (89.8)	86 (85.1)
1	10 (10.2)	15 (14.9)
Viral hepatitis markers		
HBs Ag (+)	12 (12.2)	10 (9.9)
HCV Ab (+)	39 (39.8)	36 (35.6)
Tumors, *n* (%)		
1	52 (53.1)	54 (53.5)
2	29 (29.6)	26 (25.7)
3	7 (7.1)	13 (12.9)
4	6 (6.1)	7 (6.9)
5 or more	4 (4.1)	1 (1.0)
Maximum tumor diameter, mm, *n* (%)		
Median [range]	20 [10–50]	20 [10–49]
≤30 mm	72 (73.5)	75 (74.3)
>30 mm	26 (26.5)	26 (25.7)
Vascular invasion, *n* (%)		
Vp1	0 (0)	1 (0)
Vv1	1 (0)	0 (0)
BCLC stage, *n* (%)		
A	57 (58.2)	63 (62.4)
B	30 (30.6)	22 (21.8)
C	11 (11.2)	16 (15.8)
Child-Pugh class, *n* (%)		
A5	59 (60.2)	66 (65.3)
A6	26 (26.5)	21 (20.8)
B7	11 (11.2)	10 (9.9)
B8	2 (2.0)	4 (4.0)
Ascites, *n* (%)		
Present	7 (7.1)	12 (11.9)
Median serum α-fetoprotein level, ng/mL [range]	8.3 [1.2–48,072]	8.2 [1.2–4,680]
Median serum PIVKAII level, mAU/mL [range]	4.5 [57–128,750]	28 [2.8–13,945]

TACE, transarterial chemoembolization; DEB, drug-eluting bead; cTACE, conventional TACE; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C viral antibody; Vv1, tumor thrombosis in a peripheral hepatic vein; Vp1, tumor thrombosis in a segmental branch; BCLC, Barcelona Clinic Liver Cancer group; PIVKA II, protein induced by vitamin K absence or antagonist-II.

remaining patients were evaluated by CT. Among the patients showing CR at 1 month, 9 patients (5 patients of the cTACE arm and 4 patients of DEB-TACE arm) were evaluated by MRI at the 3-month evaluation of the treatment response, and the remaining were evaluated by CT. The CR rate at 3 months was 27.6% in the DEB-TACE arm and 75.2% in the cTACE arm, and the odds ratio for CR was 7.99 (95% CI: 4.25–15.05) (Fig. 2). The difference in the CR rate between the two arms was 47.7% (95% CI: 34.6–59.4%), which was statistically significant ($p < 0.0001$). The forest plots of the CR rate at 3 months are shown in Figure 3. A similar trend was seen in almost every subgroup, except for the subgroup with a tumor diameter of more than 3 cm. The CR rate at 1 month was 35.7% in the DEB-TACE arm and 84.2% in the cTACE arm, and the odds ratio for CR was 7.30 (95% CI: 2.68–

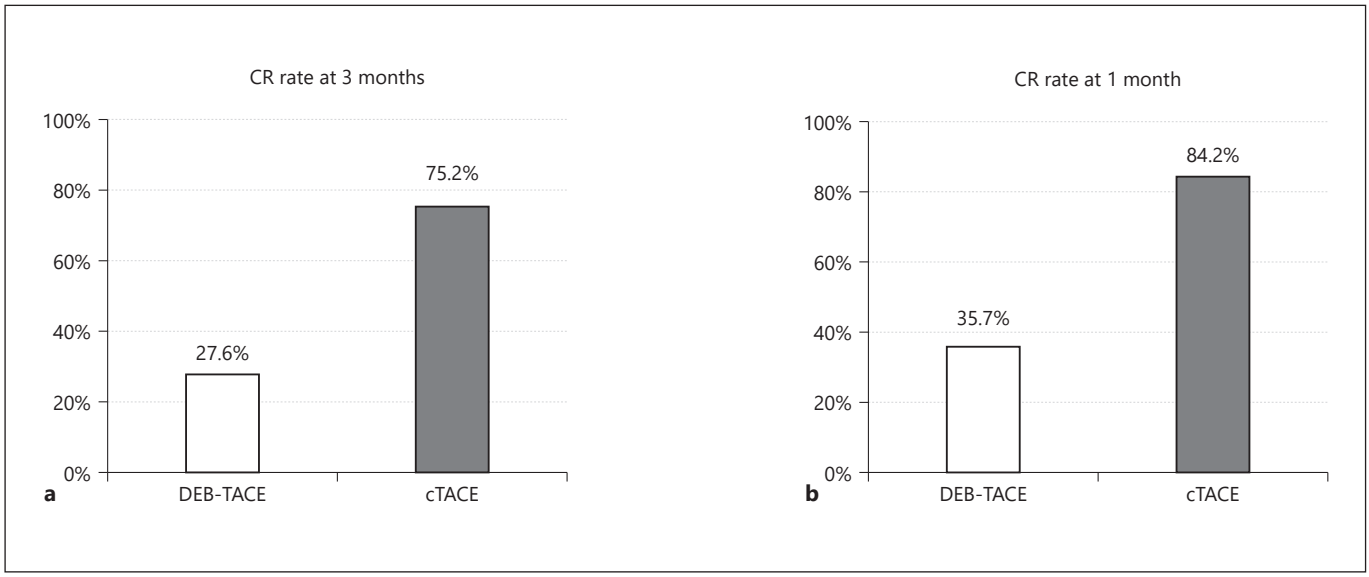

Fig. 2. a, **b** Comparison of the CR rate at 3 months and 1 month between the DEB-TACE and cTACE groups. CR rate at 3 months: odds ratio, 7.99 (95% CI: 4.25–15.05); $p < 0.0001$ (Fisher's exact test). CR rate at 1 month: odds ratio, 7.30 (95% CI: 2.68–19.89); $p < 0.0001$ (Fisher's exact test).

Table 2. TACE procedure

	DEB-TACE ($n = 98$)	cTACE ($n = 101$)
Technical success of selective TACE, *n* (%)	98 (100)	101 (100)
Dose of epirubicin, mg		
Median [range]	22.5 [1.5–150]	25 [2.3–85]
Ethiodized oil, mL		
Median [range]	–	3.0 [0.47–10]
Embolic material, *n* (%)		
DC bead®: 100–300 μm	98 (100)	–
Porous gelatin particles: 1 mm cubic	–	97 (96)
Porous gelatin particles: 2 mm cubic	–	4 (4.0)
Embolized artery, *n* (%)		
Segmental artery	13 (13.3)	4 (4.0)
Subsegmental artery	85 (86.7)	97 (96.0)
Split TACE, present,* *n* (%)	0	2 (2.0)

TACE, transarterial chemoembolization; DEB, drug-eluting bead; cTACE, conventional TACE. * The protocol treatment was repeated twice within 1 month when the treatment could not be completed in one session.

19.89) (Fig. 2). The difference in the CR rate between the two arms was 48.4% (95% CI: 35.4–59.8%), which was statistically significant ($p < 0.0001$).

Adverse Events

The adverse events in the two arms are listed in Table 3. The frequencies of pyrexia, fatigue, malaise, appetite loss, nausea, abdominal pain, hypoalbuminemia, total bilirubin increased, AST increased, and ALT increased of any grade, which constitute the so-called postembolization syndrome, were significantly higher in the cTACE arm than in the DEB-TACE arm. The frequencies of the following adverse reactions of any grade were also significantly higher in the cTACE arm than in the DEB-

TACE arm: appetite loss (cTACE vs. DEB-TACE; 28.7% vs. 12.2%, $p = 0.0048$); abdominal pain (23.8% vs. 8.2%, $p = 0.0423$); hypoalbuminemia (60.4% vs. 4.4%, $p = 0.0154$); AST increased (81.2% vs. 35.7%, $p < 0.0001$); and ALT increased (77.2% vs. 35.7%, $p < 0.0001$). As serious adverse events, the following 3 events were observed: grade 2 biloma and grade 3 biliary tract infection in 1 patient each in the DEB-TACE arm, and grade 3 liver abscess in 1 patient of the cTACE arm. There were no treatment-related deaths in either arm in this trial.

Discussion/Conclusion

The high potential efficacy of selective TACE, which is frequently performed in Asian countries [15, 16, 23, 24], is well-recognized. The EASL guideline and ESMO Clinical Practice Guidelines recommend selective TACE to increase the treatment efficacy and minimize the ischemic insult to non-tumor tissues [18, 19]. However, the optimal selection criteria for DEB-TACE and cTACE still remain unclear, and the decision is usually done based on the experience of the interventional radiologists and treating physicians. Therefore, we conducted this randomized controlled trial of selective DEB-TACE versus selective cTACE in patients with unresectable HCC to determine which of the two treatments might be more likely to yield CR. In this trial, the CR rate at 3 months as assessed by the IRC was significantly higher in the cTACE arm than in the DEB-TACE arm, and the primary endpoint was met. In addition, significant differences were also observed in almost all the subgroup analyses (Fig. 3). Selective cTACE is theoretically considered to be more effective than selective DEB-TACE (Fig. 4). In selective cTACE, the ethiodized oil can pass through the sinusoids to reach the portal vein surrounding the tumor; as a result, it can temporarily block the sinusoids, portal vein, and arterial micro-communications [5, 15, 16, 23, 24]. Therefore, ethiodized oil acts as a tiny embolic material itself, embolizing both the portal vein radicals and hepatic artery branches. On the other hand, the drug-eluting beads in selective DEB-TACE can embolize the tumor-feeding vessels at the level of the arterioles, as the diameter of the arterioles matches that of the beads (100–300 μm) but cannot reach travel via the sinusoids to the portal vein radicals. Thus, we considered that a higher CR rate might be expected from selective cTACE than from selective DEB-TACE. We conducted this trial to verify our hypothesis.

Table 3. Adverse events

	DEB-TACE ($n = 98$), n (%)				cTACE ($n = 101$), n (%)				p value*	
	grade 1	grade 2	grade 3	grade 4	grade 1	grade 2	grade 3	grade 4	any grade	grade 3–4
Pyrexia	19 (19.4)	0	0	0	40 (39.6)	6 (5.9)	0	0	0.0001	–
Fatigue	4 (4.1)	1 (1.0)	0	0	12 (11.9)	4 (4.0)	0	0	0.0194	–
Malaise	10 (10.2)	1 (1.0)	0	0	21 (20.8)	5 (5.0)	0	0	0.0103	–
Appetite loss	11 (11.2)	1 (1.0)	0	0	25 (24.8)	3 (3.0)	1 (1.0)	0	0.0048	1.0000
Nausea	8 (8.2)	1 (1.0)	0	0	13 (12.9)	0	0	0	0.4991	–
Vomiting	3 (3.1)	0	0	0	4 (4.0)	0	0	0		
Abdominal pain	8 (8.2)	4 (4.1)	0	0	16 (15.8)	7 (6.9)	1 (1.0)	0	0.0423	1.0000
WBC decreased	7 (7.1)	8 (8.2)	2 (2.1)	0	5 (5.0)	4 (4.0)	0	1 (1.0)		
Neut decreased	4 (4.1)	5 (5.1)	2 (2.1)	0	4 (4.0)	0	0	1 (1.0)		
Hb decreased	21 (21.4)	5 (5.1)	0	0	16 (15.8)	6 (5.9)	4 (4.0)	0		
Plt decreased	11 (11.2)	14 (14.3)	2 (2.1)	0	14 (13.9)	9 (8.9)	15 (14.9)	0		
Hypoalbuminemia	25 (25.5)	18 (18.4)	0	0	28 (27.7)	32 (31.9)	1 (1.0)	0	0.0154	1.0000
Bil increased	12 (12.2)	10 (10.2)	0	0	32 (31.9)	17 (16.8)	0	0	0.0002	–
AST increased	24 (24.5)	6 (6.1)	5 (5.1)	0	15 (14.9)	18 (17.8)	39 (38.6)	10 (9.9)	<0.0001	<0.0001
ALT increased	26 (26.5)	6 (6.1)	3 (3.1)	0	16 (15.8)	23 (22.8)	36 (35.6)	3 (3.0)	<0.0001	<0.0001
ALP increased	16 (16.3)	0	0	0	29 (28.7)	3 (3.0)	2 (2.0)	0		
Cr increased	9 (9.2)	2 (2.1)	0	0	8 (7.9)	0	0	0	0.8275	–

TACE, transarterial chemoembolization; DEB, drug-eluting bead; cTACE, conventional TACE; WBC, white blood cell; Neut, neutrophil; Hb, hemoglobin; Plt, platelet; Bil, serum bilirubin; AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; ALP, serum alkaline phosphatase; Cr, serum creatinine. * Fisher's exact test.

		CR rate at 3 month			
		DEB-TACE	cTACE	Odds ratio (95% CI)	*p*-value
Overall		27.6%	75.2%	7.99 (4.25–15.05)	<0.0001
Age, years	< 75	26.5%	77.6%	9.59 (3.96–23.22)	<0.0001
	>75	28.6%	72.1%	6.46 (2.60–16.05)	<0.0001
Sex	Male	30.0%	77.9%	8.24 (3.82–17.77)	<0.0001
	Female	21.4%	69.7%	8.43 (2.62–27.14)	0.0003
ECOG-PS	0	28.4%	73.3%	6.90 (3.55–13.43)	<0.0001
	1	20.0%	86.7%	26.00 (3.03–222.93)	0.0024
MBs Ag	(–)	26.7%	74.7%	8.10 (4.14–15.86)	<0.0001
	(+)	33.3%	80.0%	8.00 (1.13–56.79)	0.0427
HCV Ab	(–)	23.7%	76.9%	10.71 (4.66–24.63)	<0.0001
	(+)	33.3%	72.2%	5.20 (1.94–13.96)	0.0011
Number of tumors	1	33.3%	79.1%	7.57 (3.44–16.65)	<0.0001
	≥2	17.1%	67.6%	10.11 (3.25–31.45)	<0.0001
Maximum tumor size (mm)	≤30 mm	25.7%	80.0%	11.56 (5.30–25.19)	<0.0001
	>30 mm	32.1%	61.5%	3.38 (1.10–10.35)	0.0550
Child-Pugh score	A5+A6	28.2%	73.6%	7.07 (3.62–13.83)	<0.0001
	B7+B8	23.1%	85.7%	20.00 (2.77–144.31)	0.0018
BCLC stage	A	29.7%	78.1%	8.44 (3.90–18.25)	<0.0001
	B, C	23.5%	67.9%	6.86 (2.24–21.05)	0.0007
AFP (ng/mL)	≤8.2 (Median)	32.7%	86.3%	12.96 (4.79–35.11)	<0.0001
	>8.2 (Median)	22.4%	64.0%	6.14 (2.53–14.89)	<0.0001
PIVKAN (mAU/mL)	≤ 35 (Median)	22.7%	78.0%	12.03 (4.72–30.68)	<0.0001
	> 35 (Median)	31.5%	71.4%	5.44 (2.25–13.14)	0.0002

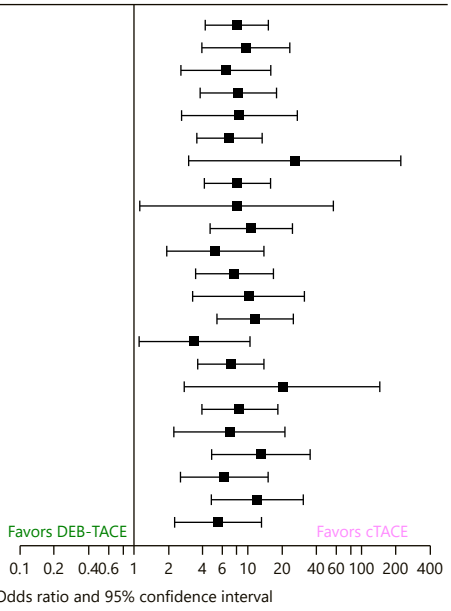

Fig. 3. Forest plots indicating the odds ratios for the CR rate in subgroup analyses.

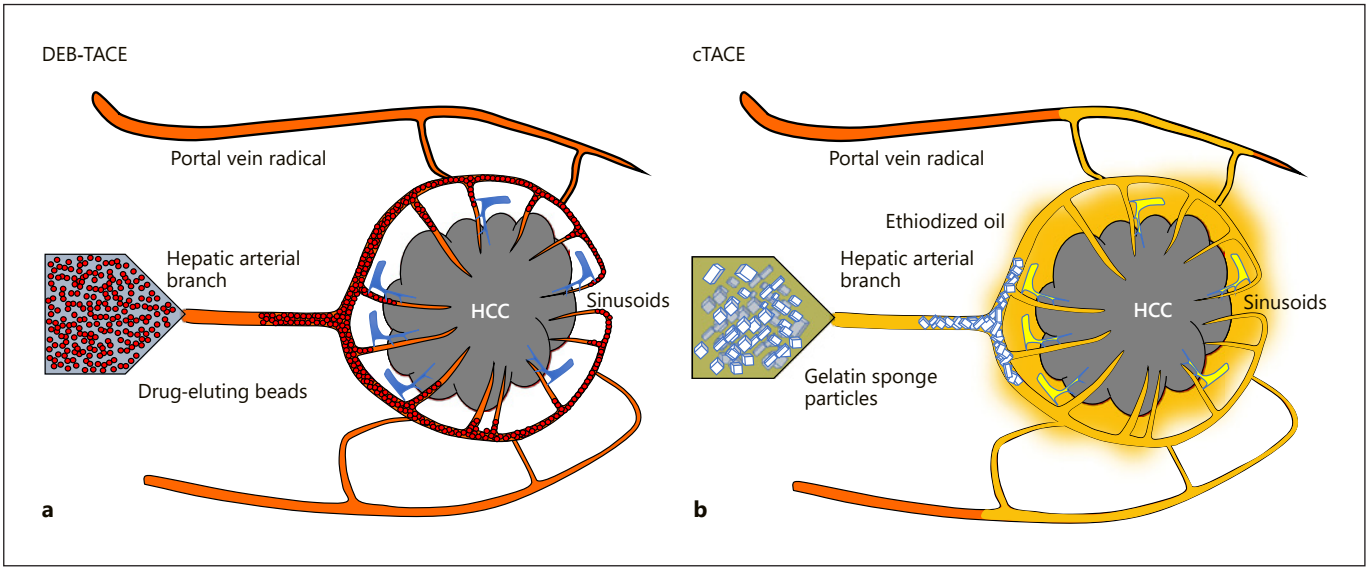

Fig. 4. Schema of the rationale for DEB-TACE and cTACE. **a** DEB-TACE. Drug-eluting beads cannot reach neighboring hepatic arterial branches that are smaller in diameter than the beads. Therefore, DEB-TACE can stop the blood supply from the hepatic arteries but cannot stop the blood supply from the portal vein and/or hepatic sinusoids. **b** cTACE. An anticancer agent emulsified in ethiodized oil can pass through the hepatic sinusoids to reach the portal vein surrounding the tumor, to temporarily block the sinusoids, portal vein, and arterial microcommunications. Then, the tumor-feeding hepatic arteries are additionally embolized using gelatin sponge particles. cTACE can stop the blood supply from the portal vein and/or hepatic sinusoids as well as the hepatic arteries.

In regard to adverse events, the frequencies of components of the postembolization syndrome, such as worsening of the liver function and systemic symptoms, were significantly higher in the cTACE arm than in the DEB-TACE arm. Even with selective treatment, the strong ischemia induced by cTACE might also affect the liver parenchyma surrounding the tumor [5, 15, 16, 23, 24]. As the result, liver damage is also more likely to occur in patients treated by cTACE, and our results are consistent with previous reports. Therefore, potential tolerance to postembolization syndrome is considered as an important criterion for determining the indication for cTACE.

This study had several limitations. First, this was an unblinded trial, and the allocated treatment was known to the investigators as well as the interventional radiologists. Also, the proportion of patients who received subsegmental TACE was slightly higher in the cTACE arm than in the DEB-TACE arm. Selective catheterization would undeniably be preferred to obtain favorable results in the cTACE arm. However, drug-eluting beads easily fill up the feeding arteries, and selective TACE via subsegmental arteries is often difficult. Second, the tumor response at 3 months and 1 month were evaluated by contrast-enhanced CT or MRI, but precise evaluation by contrast-enhanced CT might be difficult in patients treated by cTACE (using ethiodized oil). Differentiation between a viable lesion and accumulation of ethiodized oil is often difficult in these cases because ethiodized oil could cause halation of the treated lesion [27, 28]; thus, there is the possibility of the tumor response being overestimated by CT in the cTACE group. Third, in this trial, we could not compare the overall survival from the initiation of the first selective TACE between the two arms because: (1) in patients in whom one TACE method was not effective, the treatment was crossed over to the other TACE method; (2) the direct therapeutic effect of TACE could be reduced by post-treatments, including systemic therapy, in the era of advanced systemic therapies [20–22]; (3) since the number of patients who were scheduled to receive their first TACE at this early stage of the disease was very limited, patients who had already received TACE had to be included to ensure speed of enrollment. We decided not to include the overall survival as an endpoint of the study. Although this trial had some limitations, there was a greater difference in the CR rate between the two arms than we expected, and we believe that it was reasonable to conclude that selective cTACE is more likely to yield CR than selective DEB-TACE in patients with HCC.

In conclusion, selective cTACE appears to be more effective for obtaining local tumor control in patients with HCC as compared with selective DEB-TACE. However, the frequency of postembolization syndrome was also significantly higher in the cTACE group than in the DEB-TACE group. Thus, to achieve CR, cTACE may be selected over DEB-TACE in patients who can be expected to tolerate postembolization syndrome.

Acknowledgments

We thank all the patients and their families for their participation in this study. This study was supported by a grant from 26-A-27/National Cancer Center Research and Development Fund. We would like to thank Mr. Noriaki Ohba for his support with the statistical analysis and Ms. Asako Imai and Ms. Tomoko Ando of the EP-CRSU Data Center for their assistance with the data management. We would also like to thank Drs. Kiyoshi Matsueda, Yasunori Arai, Shinji Wada, Takatoshi Kubo, Shintaro Kumura, and Shinji Fujitsuka, members of the IRC. This paper was critically reviewed by a native English speaker at the Translation Division, International Medical Information Center, Tokyo.

Statement of Ethics

This clinical trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and the study protocol was approved by the Institutional Review Boards of the National Cancer Center and the participating centers. This trial is registered with UMIN-CTR, with the identification number UMIN 000021250 (https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000024439). All patients gave written informed consent for participation prior to enrollment in this trial.

Conflict of Interest Statement

M.I. reports having received personal fees and others from Bayer, Bristol-Myers Squibb, Eli Lilly, Eisai, and Chugai; personal fees from Sumitomo Dainippon, EA Pharma, and Gilead; other from Takeda Pharmaceutical, AstraZeneca, and Merck Serono during the conduct of this study; in addition, he received personal fees and other from ASLAN, Daiichi Sankyo, Novartis, Kyowa Hakko Kirin, NanoCarrier, Yakult, and Taiho; personal fees from Teijin Pharma, Shire, Nobel pharma, Otsuka, MSD, Mylan, and NIHON SERVIER; other from Baxalta, Ono, and J-Pharma outside the period of this study. Y.A. reports having received personal fees from Guerbet Japan during the conduct of this study and personal fees from Japan Lifeline, Kyorin Pharma, Canon Medical systems, and Fuji Pharma outside the period of this study. In addition, Y.A. has a patent Sumitomo Bakelite with royalties paid. Y.I. reports having received personal fees from Eisai and Guerbet Japan during the conduct of this study. T.T. reports having received personal fees from Eisai and Guerbet Japan during the conduct of this study. S.S. reports having

received personal fees from CANON MEDICAL SYSTEMS and Cosmotec Co., Ltd, outside the period of this study. Y.K. reports having received personal fees from Eisai outside the period of this study. H.S. reports having received personal fees from Eisai during the conduct of this study. M.M. reports having received personal fees from Terumo, Daiichi Sankyo, and Boston Scientific outside the period of this study. M. Sone. reports having received personal fees from Guerbet Japan during the conduct of the study and personal fees from Fuji Pharma Co., Ltd, CANON MEDICAL SYSTEMS; other from Dream Medicals outside the period of this study. Other authors have no conflicts of interests to declare in relation to this study. M.I. is an Editorial Board Member of *Liver Cancer*.

Funding Sources

This study was supported by a grant from 26-A-27/National Cancer Center Research and Development Fund.

Author Contributions

Masafumi Ikeda and Yasuaki Arai designed the original concept of the study, discussed and modified the study, collected and/or assembled data, interpreted the data, prepared the first draft of the manuscript, revised the manuscript drafts, and provided final approval of the manuscript submitted for consideration of publication. Yoshitaka Inaba, Toshihiro Tanaka, Shunsuke Sugawara, Yoshihisa Kodama, Takeshi Aramaki, Hiroshi Anai, Shinichi Morita, Yoshinori Tsukahara, Hiroshi Seki, Mikio Sato, Kenya Kamimura, Kimei Azama, Masakatsu Tsurusaki, Eiji Sugihara, Masaya Miyazaki, Tatsushi Kobayashi, and Miyuki Sone conceived the design of the study, collected and/or assembled data, interpreted the data, performed critical reviews of the manuscript drafts, and provided final approval of the manuscript submitted for consideration of publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018.
2 Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002;224:47–54.
3 Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429–42.
4 Ikeda M, Arai Y, Park SJ, Takeuchi Y, Anai H, Kim JK, et al. Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian cooperative study between Japan and Korea. J Vasc Interv Radiol. 2013;24:490–500.
5 de Baere T, Arai Y, Lencioni R, Geschwind JF, Rilling W, Salem R, et al. Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. Cardiovasc Intervent Radiol. 2016;39:334–43.
6 Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52.
7 Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 2014;111:255–64.
8 Sacco R, Bargellini I, Bertini M, Bozzi E, Romano A, Petruzzi P, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2011;22:1545–52.
9 van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie. 2011;34:368–76.
10 Zou JH, Zhang L, Ren ZG, Ye SL. Efficacy and safety of cTACE versus DEB-TACE in patients with hepatocellular carcinoma: a meta-analysis. J Dig Dis. 2016;17:510–7.
11 Yang B, Liang J, Qu Z, Yang F, Liao Z, Gou H. Transarterial strategies for the treatment of unresectable hepatocellular carcinoma: a systematic review. PLoS One. 2020;15:e0227475.
12 Han T, Yang X, Zhang Y, Li G, Liu L, Chen T, et al. The clinical safety and efficacy of conventional transcatheter arterial chemoembolization and drug-eluting beads-transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a meta-analysis. Biosci Trends. 2019;13(5):374–81.
13 Huang K, Zhou Q, Wang R, Cheng D, Ma Y. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma. J Gastroenterol Hepatol. 2014;29:920–5.
14 Chen P, Yuan P, Chen B, Sun J, Shen H, Qian Y. Evaluation of drug-eluting beads versus conventional transcatheter arterial chemoembolization in patients with unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2017;41:75–85.
15 Matsui O, Kadoya M, Yoshikawa J, Gabata T, Arai K, Demachi H, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology. 1993;188:79–83.
16 Miyayama S, Matsui O, Yamashiro M, Ryu T, Kaito K, Ozaki H, et al. Ultraselective transcatheter arterial chemoembolization with a 2-f tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. J Vasc Interv Radiol. 2007;18:365–76.
17 Golfieri R, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology. 2011;53:1580–9.
18 European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.
19 Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv238–55.
20 Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018;15:599–616.

21 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894–905.
22 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–73.
23 Kim BK, Kim SU, Kim KA, Chung YE, Kim MJ, Park MS, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol. 2015;62(6):1304–10.
24 Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific primary liver cancer expert consensus statements. Liver Cancer. 2020;9:245–60.
25 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.
26 Lencioni R, de Baere T, Burrel M, Caridi JG, Lammer J, Malagari K, et al. Transcatheter treatment of hepatocellular carcinoma with doxorubicin-loaded DC bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol. 2012;35:980–5.
27 Chiu RY, Yap WW, Patel R, Liu D, Klass D, Harris AC. Hepatocellular carcinoma post embolotherapy: imaging appearances and pitfalls on computed tomography and magnetic resonance imaging. Can Assoc Radiol J. 2016;67:158–72.
28 Kubota K, Hisa N, Nishikawa T, Fujiwara Y, Murata Y, Itoh S, et al. Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization: comparison of Lipiodol-CT, power Doppler sonography, and dynamic MRI. Abdom Imaging. 2001;26:184–90.