Imaging Changes and Clinical Complications After Drug-Eluting Bead Versus Conventional Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: Multicenter Study

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Keywords

hepatocellular carcinoma, retrospective study, safety, therapeutic chemoembolization

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BACKGROUND. Drug-eluting bead transarterial chemoembolization (DEB-TACE) has emerged as an alternative to conventional TACE (cTACE) for treatment of hepatocellular carcinoma (HCC), although selection between the approaches remains controversial.

OBJECTIVE. The purpose of this study was to compare DEB-TACE and cTACE in the treatment of patients with unresectable HCC in terms of hepatobiliary changes on imaging and clinical complications.

METHODS. This retrospective study included 1002 patients (871 men, 131 women; mean age, 59 ± 12 years) from three centers who had previously untreated unresectable HCC and underwent DEB-TACE with epirubicin (780 procedures in 394 patients) or cTACE with ethiodized oil mixed with doxorubicin and oxaliplatin (1187 procedures in 608 patients) between May 2016 and November 2018. Among these patients 83.4% had hepatitis B–related liver disease, 57.6% had Barcelona Clinic Liver Cancer (BCLC) stage A or B HCC, and 42.4% had three or more nodules. Mean tumor size was 6.3 ± 4.2 cm. Hepatobiliary changes and tumor response were evaluated with CT or MRI 1 month after TACE. Clinical records were reviewed for adverse events.

RESULTS. Bile duct dilatation ($p < .001$) and portal vein narrowing ($p = .006$) on imaging and liver failure ($p = .03$) and grade 3 abdominal pain ($p < .001$) in clinical follow-up occurred at higher frequency in the DEB-TACE group (15.5%, 4.6%, 2.3%, and 6.1%) than in the cTACE (7.4%, 1.6%, 0.7%, and 2.1%) group. Higher frequency of bile duct dilation in patients who underwent DEB-TACE was observed in subgroup analyses that included patients with BCLC stage A or B HCC ($p = .001$), with cirrhosis ($p < .001$), without cirrhosis ($p = .04$), and without main portal vein tumor thrombus ($p = .002$). Total bilirubin level 1 month after treatment was 1.5 ± 2.4 mg/dL (95% CI, 1.2–1.8 mg/dL) for DEB-TACE versus 1.3 ± 2.0 mg/dL (95% CI, 1.1–1.5 mg/dL) for cTACE ($p = .02$). The cTACE and DEB-TACE groups did not differ in other manifestations of postembolization syndrome or systemic toxicity ($p > .05$). Local tumor disease control rates did not differ between the cTACE and DEB-TACE groups (1 month, 96.7% vs 98.5%, $p = .06$; 3 months, 81.8% vs 82.4%, $p = .87$), but overall DCR was significantly higher in the cTACE than in the DEB-TACE group (1 month, 87.5% vs 80.0%, $p = .001$; 3 months, 78.5% vs 72.1%, $p = .02$).

CONCLUSION. Compared with cTACE, DEB-TACE was associated with greater frequency of hepatobiliary injury and severe abdominal pain.

CLINICAL IMPACT. Greater caution and closer follow-up are warranted for patients who undergo DEB-TACE for unresectable HCC than for those who undergo cTACE.

Primarily on the basis of the results of two randomized controlled trials [1–3], transarterial chemoembolization (TACE) has become the standard approach to the management of intermediate-stage hepatocellular carcinoma (HCC), classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Real-world data, however, show that TACE is widely used not only for intermediate-stage but also for advanced HCC [4].

Conventional TACE (cTACE) combines cytotoxic and ischemic effects by intraarterial injection of concentrated chemotherapeutic solutions in ethiodized oil (Lipiodol, Guerbet). This oil is an optimal agent because of its preferential uptake by the tumor [5]. However, inconsistent drug delivery and retention limit the long-term outcome of TACE [2, 3,

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6]. Drug-eluting bead TACE (DEB-TACE) has emerged as an alternative approach to HCC treatment [7, 8]. Previous studies [9, 10] have shown that administration in DEBs may prolong release of chemotherapeutic drugs and decrease the systemic concentration of these agents.

Theoretically, DEB-TACE should afford a better outcome than cTACE [11]. A 2019 meta-analysis [12] showed that patients with HCC who undergo DEB-TACE may have more favorable outcomes than those who undergo cTACE. However, neither the Prospective Randomised Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolisation (PRECISION V) [9] nor the PRECISION Italia Study Group trial [13] met the superiority endpoint for patients who underwent DEB-TACE. Another meta-analysis that included 693 patients [14] also showed no superiority of DEB-TACE over cTACE in terms of efficacy and safety. Conversely, results of two studies [15, 16] suggested that liver or biliary injury, biloma, or liver infarct—based on imaging findings—were independently associated with DEB-TACE. In this regard, the choice between DEB-TACE and cTACE for the treatment of HCC remains controversial [17]. Compared with data on cTACE, limited data are available for comprehensively describing clinical complications and imaging changes associated with DEB-TACE.

Our aim was to compare DEB-TACE and cTACE for the treatment of patients with unresectable HCC in terms of hepatobiliary changes on imaging and clinical complications.

Methods

Patient Selection

This multicenter retrospective study included patients with HCC who were treated with DEB-TACE or cTACE as initial treatment at three centers between May 2016 and November 2018. The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the institutional review boards at all three participating centers. The requirement for written informed consent was waived.

A review of electronic medical records at the three centers to find adult patients with unresectable HCC who underwent TACE [18] initially identified 3867 potentially eligible patients. The diagnosis of HCC was based on the diagnostic criteria of the European Association for the Study of the Liver or the American Association for the Study of Liver Diseases [5, 19]. Patients were excluded for the following reasons: prior treatment of HCC (n = 2287); history of other malignancy or diagnosis of other concurrent malignancy (n = 37); missing clinical or imaging follow-up information (n = 223); Eastern Cooperative Oncology Group performance status greater than 1 (n = 76); decompensated liver function (defined as bilirubin level > 3 mg/dL or aspartate aminotransferase [AST] or alanine aminotransferase [ALT] level more than 5 times the upper limit of normal or > 250 U/L) (n = 94), which is a contraindication to TACE; or surgery or ablation performed in the 3-month follow-up period after TACE (n = 148). These exclusions left a final sample of 1002 patients (Fig. 1).

A multidisciplinary discussion was held to decide whether TACE was the optimal treatment of each patient. The choice of DEB-TACE or cTACE was based on physician assessment and patient and family member agreement after they were informed of the potential advantages, disadvantages, and costs of DEB-TACE and cTACE.

HIGHLIGHTS

Key Finding

- *In a retrospective multicenter study that included 1002 patients with unresectable HCC, frequencies of bile duct dilation, portal vein narrowing, liver failure, and abdominal pain were higher ($p < .05$) in patients treated with DEB-TACE (15.5%, 4.6%, 2.3%, 6.1%) than in those treated with cTACE (7.4%, 1.6%, 0.7%, 2.1%).*

Importance

- *Compared with cTACE, DEB-TACE for previously untreated HCC is associated with higher frequency of hepatobiliary injury but similar short-term local control.*

Transarterial Chemoembolization Procedures

Both DEB-TACE and cTACE cycles were performed by an on-demand approach, that is, repeat procedures were performed only to treat residual or new tumor [20]. Local anesthesia was administered by injection of 5 mL lidocaine into the subcutaneous tissue of the groin. Before chemoembolization, diagnostic angiography was performed to evaluate portal vein patency and presence of hepatopetal flow to determine the arterial supply of the tumor and hepatic artery anatomy. Segmental or subsegmental procedures were performed with a 2.7-French microcatheter (Progreat, Terumo) to target the tumor-feeding arteries and to decrease damage to nontumor liver.

In the DEB-TACE group, patients received a dose of 2–4 mL DC Bead (Biocompatibles) or CalliSphere (Jiangsu Hengrui Medicine) beads with a diameter of 100–300 or 300–500 μm. The selection of DEBs depended on physician preference and the diameter of the tumor vessels (for tumor vessels smaller than 2 mm, 100–300 μm was selected [21]). Epirubicin dose depended on the extent of liver tumor burden and hepatic reserve; the maximum dose was 100 mg per patient. The target vessels were slowly emboli-

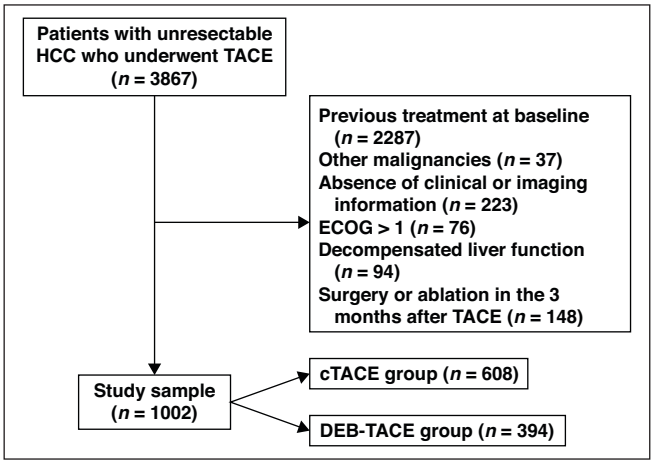

Fig. 1—Flowchart shows selection of study sample. HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, ECOG = Eastern Cooperative Oncology Group, cTACE = conventional TACE, DEB-TACE = drug-eluting bead TACE.

zed with a 1 mL/min injection of the DEBs (embolic agent mixed with chemotherapeutic reagent solution) mixed with an equal volume of nonionic contrast agent (total of 15–30 mL), The endpoint of embolization was near-stasis in the tumor feeding vessel, which was generally achieved by the time the contrast agent cleared (2–5 heartbeats). Additional unloaded Embosphere particles (Merit Medical) were used to complete the procedure if the endpoint was not achieved after the injection of DEBs.

In the cTACE group, patients were treated by intraarterial administration of doxorubicin (20–40 mg/m^2) and oxaliplatin (85 mg/m^2) mixed with ethiodized oil (2–20 mL Lipiodol Ultra Fluid, 480 mg I/mL) in a 1:3 ratio followed by injection of another bead agent, such as gelatin foam particles (Gelfoam, Hangzhou Aili Kang Pharmaceutical Technology), polyvinyl alcohol particles, or Embosphere microspheres (Merit Medical). The doses of doxorubicin and oxaliplatin were administrated in the same manner as for DEB-TACE. The endpoint of embolization was observation of stagnant flow in the feeding arterial vessels. For patients with larger tumors (at the treating physician's discretion, though generally > 5 cm), additional embolization with the same particle size and embolic agent was performed if the endpoint was not achieved. After 5 minutes, angiography was repeated to determine whether stasis in a segmental or subsegmental vessel was achieved.

Imaging and Clinical Endpoints

All laboratory indexes were measured before the procedure and 3 and 7 days and 1 month after the procedure. Multiphase CT or MRI was performed within 1 month after the procedure and every 2–3 months thereafter by use of the same modality. The details of CT and MRI protocols are presented in Supplemental Methods (available in the *AJR* electronic supplement to this article at doi.org/10.2214/AJR.20.24708). The hospital discharge note and the routine interventional radiology clinic note 1 month after TACE were used to document adverse events occurring after the procedure. The date of last follow-up evaluation was March 31, 2019.

Baseline and follow-up CT and MRI were assessed independently by two radiologists (G.Z. and J.H.S., 8 and 7 years of experience in abdominal imaging) at a PACS workstation (Neusoft PACS/RIS, Shengyang Neusoft). The readers were blinded to patient demographics and treatment administered. A third radiologist (Z.L., 15 years of experience in abdominal imaging) resolved disagreements between the first two readers.

The primary outcomes were imaging changes and clinical complications occurring within 1 month after the procedure. Imaging changes assessed on preoperative and postoperative CT or MRI included dilated bile duct, portal vein narrowing, portal vein thrombosis, intrahepatic biloma, liver infarct, and cholecystitis [16]. The imaging changes were considered present for purposes of this investigation only when they were new after TACE; they were thus deemed to represent liver or biliary injury due to the procedure.

With the exception of nearby tumor invasion and compression, bile duct dilatation was defined as increased diameter of the bile duct after TACE in comparison with pre-TACE imaging, appearing as linear hypoattenuation adjacent to the portal vein on CT or hyperintensity adjacent to the portal vein on T2-weighted MRI [22, 23]. Portal vein narrowing was defined as decreased diameter of the first- or second-order portal vein branch compared with the diameter on pre-TACE imaging with preservation of the intraluminal flow surrounding the area of hypoattenuation on CT or hyperintensity on T2-weighted MRI [24]. Portal vein thrombus was defined as absence of contrast enhancement of or inability to visualize the portal vein branch. Intrahepatic biloma was defined as round, solitary or multiple, cystic areas in the nontumor parenchyma that communicated with the bile duct without enhancement in any phase of follow-up CT or MRI [16, 25]. Liver infarct was defined as an irregular or wedge-shaped hypoattenuating area adjacent to the bile duct without enhancement on CT or MRI [15].

Clinical complications included liver toxicity, postembolization syndrome, and systemic toxicity. Liver toxicity was defined as elevated AST, ALT, or total bilirubin level or as liver-related complications, including liver failure (elevation of bilirubin level three times the baseline value or elevation of ALT or AST level five times the baseline value within 1 month after TACE), liver abscess, hepatorenal syndrome, or other severe hepatic infection. Postembolization syndrome was defined as postprocedural fever, fatigue, abdominal pain, abdominal distention, nausea, emesis, hiccups, or constipation. Systemic toxicity was defined as granulopenia, bone marrow suppression, thrombocytopenia, hypoalbuminemia, increased international normalized ratio, or post-TACE ascites. Liver toxicity, postembolization syndrome, and systemic toxicity were assessed according to the Common Terminology Criteria for Adverse events, version 5.0. Severe adverse events were also recorded, defined as events leading to death, immediately life-threatening events, or events resulting in disability, incapacity, or prolonged hospital admission.

The secondary outcome was short-term efficacy. Tumor response was evaluated with either CT or MRI in terms of both local (per lesion) response and overall (per patient) response, according to the modified RECIST (mRECIST) 1 and 3 months after TACE. Disease control rate (DCR) and objective response rate (ORR) were defined as in previously published studies [26, 27].

Statistical Analysis

Continuous variables were expressed as mean ± SD and categoric variables as number and percentage. Continuous variables were compared between the groups and subgroups by two-sided *t* test or Kruskal-Wallis test. Categoric variables were compared by Fischer exact test. Two-tailed $p < .05$ was considered statistically significant. Logistic regression analyses were used to calculate the corresponding odds ratio with 95% CIs and to analyze the risk factors (TACE type, presence of cirrhosis, BCLC stage, and Child-Pugh score) associated with liver or biliary injuries and liver-related complications. Variables with $p < .05$ in univariable analysis were considered dependent variables and were further assessed in multivariable analysis. All statistical tests were performed with SPSS software (version 20.0 for Microsoft Windows, IBM).

Results

A total of 1002 patients (871 men, 131 women; mean age, 59 ± 12 years) were included. A total of 83.4% of patients had positive hepatitis B surface antigen results. Mean tumor size was 6.3 ± 4.2 cm. A total of 57.6% of patients had BCLC stage A or B HCC. A total of 1967 TACE procedures were performed: 1187 cTACE in 608 patients and 780 DEB-TACE in 394 patients. In the cTACE group, the mean volume of ethiodized oil was 9.5 ± 6.2 mL per procedure

(range, 2–20 mL). In the DEB-TACE group, 213 patients were treated with 100- to 300-μm DC Bead microspheres and 181 with 300- to 500-μm CalliSphere beads. Table 1 shows the baseline characteristics stratified by treatment (cTACE vs DEB-TACE), and Table S1 shows the baseline characteristics stratified among the three centers. (Table S1 can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708.) Patients undergoing cTACE were younger than patients undergoing DEB-TACE (58 ± 11 years vs 61 ± 12 years; $p < .001$). The two groups also had significantly different ($p = .01$) distributions of BCLC stage. In the cTACE group, the distribution was stage A, 11.0%, B, 49.7%; C, 39.3%. In the DEB-TACE group, the distribution was stage A, 12.9%; B, 39.8%; C, 47.2%.

Liver or Biliary Injury and Liver Toxicity

Liver or biliary injuries are shown in Table 2. The most common such injuries were bile duct dilation (109 patients) (Fig. 2A), portal vein narrowing (28 patients) (Fig. 2B), and cholecystitis (24 patients). Bile duct dilation (15.5%; $p < .001$), portal vein narrowing (4.6%; $p = .006$), and liver failure (2.3%; $p < .03$) were all significantly more common in the DEB-TACE group than in the cTACE group.

TABLE 1: Baseline Characteristics of Included Patients

Characteristic	cTACE ($n = 608$)	DEB-TACE ($n = 394$)	*p*
Center			.56
A	124 (20.4)	82 (20.8)	
B	346 (56.9)	234 (59.4)	
C	138 (22.7)	78 (19.8)	
Sex			.63
Male	531 (87.3)	340 (86.3)	
Female	77 (12.7)	54 (13.7)	
Age (y)	58 ± 11	61 ± 12	< .001
Liver disease			.35
HBV	520 (85.5)	316 (80.2)	
HCV	8 (1.3)	6 (1.5)	
Alcohol	44 (7.2)	18 (4.6)	
Other	36 (5.9)	54 (13.7)	
Cirrhosis	455 (74.8)	293 (74.4)	.87
Tumor distribution			.56
Unilobar	376 (61.8)	255 (64.7)	
Bilobar	232 (38.2)	139 (35.2)	
No. of nodules			.47
1	294 (48.3)	193 (49.0)	
2	60 (9.9)	30 (7.6)	
≥ 3	254 (41.8)	171 (43.4)	
Largest nodule size (cm)	6.2 ± 4.4	6.6 ± 3.8	.09
Portal vein invasion			.05
Main portal vein	48 (7.9)	62 (15.7)	
First branch	141 (23.2)	119 (30.2)	
Second branch	38 (6.3)	53 (13.5)	
Hepatic vein invasion	63 (10.4)	40 (10.1)	> .99
ECOG performance status			.08
0	503 (82.7)	342 (86.8)	
1	105 (17.3)	52 (13.2)	
Child-Pugh Class			.23
A	449 (73.8)	305 (77.4)	
B	159 (26.2)	89 (22.6)	

(Table 1 continues on next page)

TABLE 1: Baseline Characteristics of Included Patients (continued)

Characteristic	cTACE (*n* = 608)	DEB-TACE (*n* = 394)	*p*
BCLC stage			.01
A	67 (11.0)	51 (12.9)	
B	302 (49.7)	157 (39.8)	
C	239 (39.3)	186 (47.2)	
Treatment location			
Segmental	258 (42.4)	180 (45.7)	.33
Subsegmental	350 (57.6)	214 (54.3)	
Chemoembolization reagent (mg)			
Doxorubicin	22.9 ± 16.1		
Epirubicin		62.3 ± 14.0	
Oxaliplatin	80.8 ± 25.3		
Laboratory index			
Platelet cont (10^9/L)	135.6 ± 75.1	140.9 ± 76.3	.28
Total bilirubin level (mg/dL)	1.1 ± 1.1	1.1 ± 0.6	.48
α-Fetoprotein level (ng/mL)	1158.6 ± 2181.6	1056.6 ± 1960.1	.26
Additional embolic agent			
Embosphere particles (Merit Medical)	114 (18.8)	47 (11.9)	.04
Polyvinyl alcohol	95 (15.6)	34 (8.6)	
Gelatin foam	10 (1.6)	0	
Ethiodized oil (mL)		9.5 ± 6.2	

Note—Data are number of patients with percentage in parentheses or mean ± SD. TACE = transarterial chemoembolization, cTACE = conventional TACE, DEB-TACE = drug-eluting bead TACE, HBV = hepatitis B virus, HCV = hepatitis C virus, ECOG = Eastern Cooperative Oncology Group, BCLC = Barcelona Clinic Liver Cancer.

TABLE 2: Liver or Biliary Injury and Liver-Related Complications

Condition	DEB-TACE by Bead Size (μm)			Overall DEB-TACE (*n* = 394)[a]	cTACE (*n* = 608)	*p*
	100–300 (*n* = 213)	300–500 (*n* = 181)	*p*			
Dilated bile duct	31 (14.6)	30 (16.6)	.58	61 (15.5)	45 (7.4)	< .001
Portal vein narrowing	7 (3.3)	11 (6.1)	.19	18 (4.6)	10 (1.6)	.006
Portal vein thrombus	5 (2.4)	4 (2.1)	> .99	9 (2.3)	6 (1.0)	.10
Intrahepatic biloma	2 (0.9)	1 (0.6)	> .99	3 (0.8)	0 (0.0)	.06
Liver infarct	5 (2.4)	1 (0.6)	.30	6 (1.5)	2 (0.3)	.06
Cholecystitis	2 (0.9)	10 (5.5)	.008	12 (3.0)	12 (2.0)	.28
Hepatic encephalopathy	0 (0.0)	1 (0.6)	.94	1 (0.3)	3 (0.5)	> .99
Liver failure	3 (1.4)	6 (3.3)	.36	9 (2.3)	4 (0.7)	.03
Liver abscess	8 (3.8)	1 (0.6)	.05	9 (2.3)	6 (1.0)	.06
Other severe infection	1 (0.5)	1 (0.6)	> .99	2 (0.5)	2 (0.3)	.65
Hepatorenal syndrome	2 (0.9)	1 (0.6)	> .99	3 (0.8)	1 (0.2)	.31

Note—Values are number of patients with percentage in parentheses. TACE = transarterial chemoembolization, cTACE = conventional TACE, DEB-TACE = drug-eluting bead TACE.
[a]Two patients in the DEB-TACE group died.

Subgroup analyses of data on patients with BCLC stages A and B HCC ($p = .001$), patients with cirrhosis ($p < .001$), patients without cirrhosis ($p = .04$), and patients without main portal vein tumor thrombus ($p = .002$) all showed significantly higher frequency of bile duct dilation in patients undergoing DEB-TACE than in patients undergoing cTACE (Tables S2–S5, which can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708). Bile duct dilation was also significantly more common in patients who underwent DEB-TACE than in patients who underwent cTACE with additional embolization

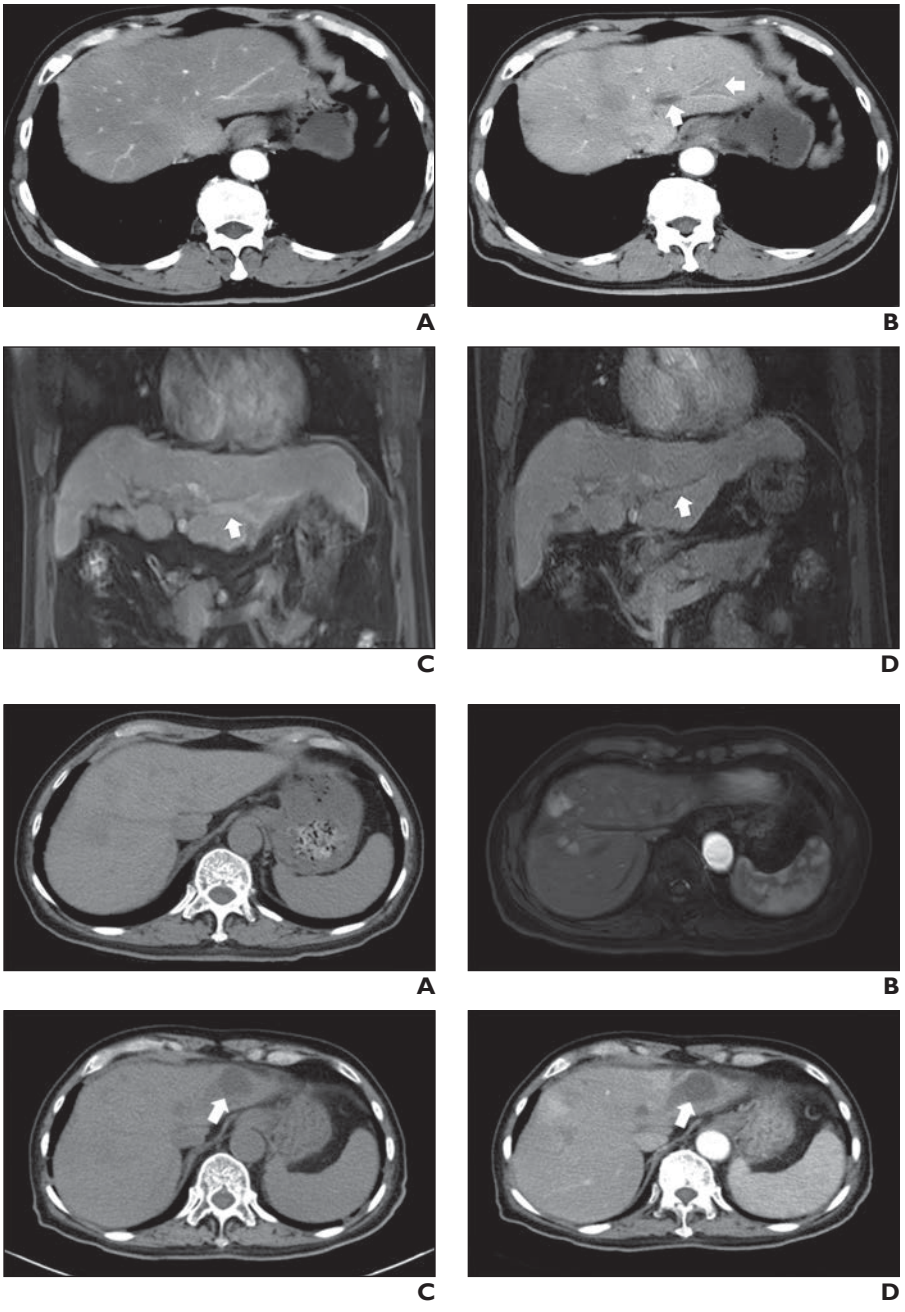

Fig. 2—Examples of liver or biliary injuries after drug-eluting bead transarterial chemoembolization (DEB-TACE).
A and **B,** 77-year-old man with hepatocellular carcinoma. Axial arterial phase CT before (**A**) and after (**B**) one session of DEB-TACE shows dilatation of bile duct (*arrows*, **B**) after treatment.
C and **D,** 58-year-old man with hepatocellular carcinoma. Coronal MRI before (**C**) and after (**D**) one session of DEB-TACE shows narrowing of portal vein (*arrow*) after treatment.

Fig. 3—65-year-old man with hepatocellular carcinoma.
A and **B,** Axial unenhanced CT (**A**) and arterial phase MRI (**B**) before drug-eluting bead transarterial chemoembolization (DEB-TACE).
C and **D,** Axial unenhanced (**C**) and arterial phase (**D**) CT after one session of DEB-TACE shows 4-cm biloma (*arrow*, **C** and **D**) of left liver lobe without enhancement after injection of iodinated contrast material.

(15.5% vs 4.1%; $p < .001$) (Table S6, which can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708). The frequency of intrahepatic biloma (Fig. 3) was 0.8% in the DEB-TACE group versus 0.0% in the cTACE group ($p = .06$). The frequency of liver infarct was 1.5% in the DEB-TACE group versus 0.3% in the cTACE group ($p = .06$). Comparison of data on patients receiving DEB-TACE with 100- to 300-μm beads with data on patients receiving 300- to 500-μm beads showed no significant differences aside from a higher frequency of cholecystitis in the 300- to 500-μm group (5.5% vs 0.9%; $p = .008$). Among patients with main portal vein tumor thrombus, none of the assessed features exhibited significant differences (all $p > .10$) between the DEB-TACE and cTACE groups (Table S7, which can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708).

Table S8 shows the results of univariable logistic regression analyses of various liver or biliary injuries and liver-related complications. (Table S8 can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708.) Table 3 shows the results of subsequent multivariable logistic regression analyses. DEB-TACE had a significant independent association with dilated bile duct (odds ratio, 2.3 [95% CI, 1.5–3.4]). Presence of cirrhosis had a significant independent inverse association with liver abscess (odds ratio, 0.3 [95% CI, 0.1–0.8]). No assessed variable was significantly associated with intrahepatic biloma or liver infarct in the regression analyses (all $p > .05$).

TABLE 3: Results of Univariable and Multivariable Analyses of Liver or Biliary Injury and Liver-Related Complications

Condition	Univariable			Multivariable		
	OR	95% CI	*p*	OR	95% CI	*p*
Dilated bile duct						
cTACE	1.0					
DEB-TACE	2.3	1.5–3.4	< .001	2.3	1.5–3.5	< .001
Liver abscess						
Noncirrhotic liver	1.0					
Cirrhotic liver	0.3	0.1–0.8	.02	0.3	0.1–0.8	.02

Note—OR = odds ratio, cTACE = conventional transarterial chemoembolization, DEB-TACE = drug-eluting bead TACE.

In both the DEB-TACE and the cTACE groups, AST and ALT levels had increased substantially 3 days after TACE. They decreased from the 3-day peak 7 days after TACE and returned to baseline 1 month after treatment (Fig. 4). In both groups, total bilirubin level had increased progressively 3 and 7 days after TACE. Although it was returning toward baseline 1 month after treatment in both groups, total bilirubin level was higher 1 month after treatment in the DEB-TACE group than in the cTACE group (1.5 ± 2.4 mg/dL [95% CI, 1.2–1.8 mg/dL] vs 1.3 ± 2.0 mg/dL [95% CI, 1.1–1.5]; $p = .02$) (Fig. 4).

The two independent readers disagreed on CT and MRI interpretation for liver or biliary injury in 9 of the 1002 patients: bile duct dilation, four patients; portal vein narrowing, two patients; portal vein thrombus, two patients; liver infarct, one patient. These discrepancies were resolved by the third reader.

Postembolization Syndrome and Systemic Toxicity

Table 4 shows findings regarding postembolization syndrome and systemic toxicity. For all assessed adverse events, at least 80% of observed instances were grade 1 or grade 2 in both groups. The only event with a significant difference in distribution between groups was abdominal pain (grades 1, 2, and 3 in the cTACE group, 28.8%, 20.1%, and 2.1%; in the DEB-TACE group, 17.5%, 31.7%, and 6.1%; $p < .001$). Severe adverse events included liver abscess, severe abdominal pain, acute liver function failure, severe infection,

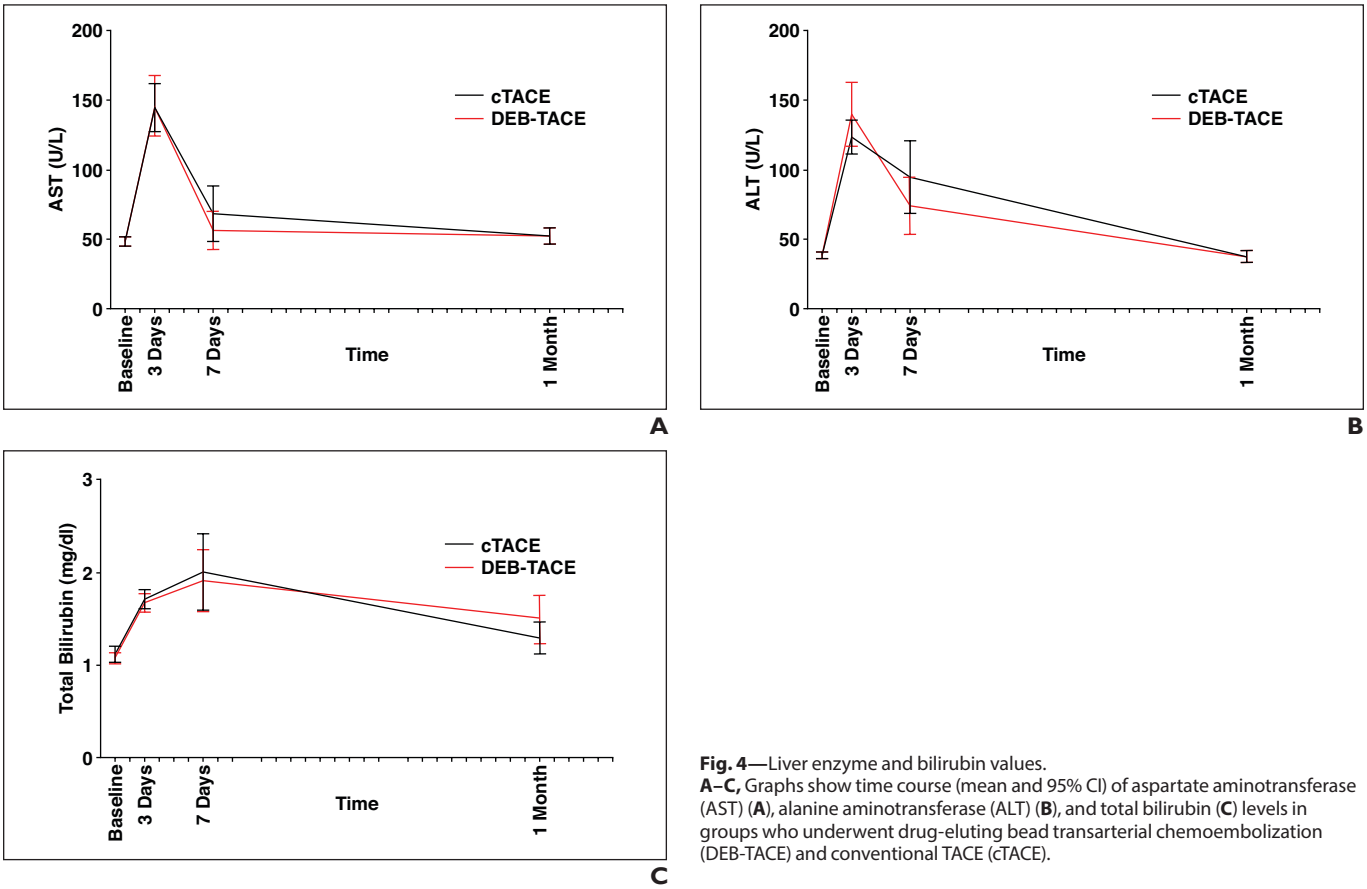

Fig. 4—Liver enzyme and bilirubin values.
A–C, Graphs show time course (mean and 95% CI) of aspartate aminotransferase (AST) (**A**), alanine aminotransferase (ALT) (**B**), and total bilirubin (**C**) levels in groups who underwent drug-eluting bead transarterial chemoembolization (DEB-TACE) and conventional TACE (cTACE).

TABLE 4: Postembolization Syndrome and Systemic Toxicity

Adverse Event and Grade	cTACE (*n* = 608)	DEB-TACE (*n* = 394)	*p*
Fever			.16
1	195 (32.1)	181 (45.9)	
2	88 (14.5)	66 (16.8)	
3	11 (1.8)	4 (1.0)	
4	2 (0.3)	0 (0.0)	
Fatigue			.91
1	39 (6.4)	23 (5.8)	
2	7 (1.2)	4 (1.0)	
Abdominal pain			< .001
1	175 (28.8)	69 (17.5)	
2	122 (20.1)	125 (31.7)	
3	13 (2.1)	24 (6.1)	
Abdominal distention			.41
1	48 (7.9)	37 (9.4)	
Nausea			.14
1	62 (10.2)	47 (11.9)	
2	12 (2.0)	15 (3.8)	
Emesis			.67
1	65 (10.7)	43 (10.9)	
2	8 (1.3)	8 (2.0)	
Hiccups			.54
1	5 (0.8)	2 (0.5)	
2	4 (0.7)	1 (0.3)	
Constipation			.23
1	79 (13.0)	65 (16.5)	
2	13 (2.1)	11 (2.8)	
Granulopenia			.06
1	24 (4.0)	9 (2.3)	
2	10 (1.6)	2 (0.5)	
3	2 (0.3)	0 (0.0)	
Bone marrow suppression			.54
1	4 (0.7)	2 (0.5)	
2	4 (0.7)	1 (0.3)	
Thrombocytopenia			.81
1	117 (19.2)	65 (16.5)	
2	119 (19.6)	73 (18.5)	
3	80 (13.2)	45 (11.4)	
4	16 (2.6)	6 (1.5)	
Hypoalbuminemia			.16
1	202 (33.2)	146 (37.1)	
2	132 (21.7)	88 (22.3)	

(Table 4 continues on next page)

TABLE 4: Postembolization Syndrome and Systemic Toxicity (continued)

Adverse Event and Grade	cTACE (*n* = 608)	DEB-TACE (*n* = 394)	*p*
Increased INR			.43
1	116 (19.1)	67 (17.0)	
2	1 (0.2)	1 (0.3)	
Post-TACE ascites			.48
1	15 (2.5)	11 (2.8)	
2	8 (1.3)	3 (0.8)	

Note—TACE = transarterial chemoembolization, cTACE = conventional TACE, DEB-TACE = drug-eluting bead TACE, INR = international normalized ratio.

gastrointestinal bleeding, intratumoral bleeding, hepatorenal syndrome, and hepatic encephalopathy (Fig. S1, which can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708). Two patients, both in the DEB-TACE group, died 2 weeks and 3 weeks after the procedure, the first of liver failure and the second of severe infection.

Treatment Response

Local tumor response and overall tumor response are summarized in Figure S2. (Fig. S2 can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708.) For local tumor response, DCR and ORR were not different between the cTACE and DEB-TACE groups 1 and 3 months after the procedure (DCR at 1 month, 98.5% vs 96.7%, (p = .06); ORR at 1 month, 61.7% vs 67.0% (p = .09); DCR at 3 months, 82.4% vs 81.8% (p = .87); and ORR at 3 months, 64.1% vs 67.3% (p = .31). For overall tumor response, DCR was significantly higher in the cTACE group than in the DEB-TACE group (1 month, 87.5% vs 80.0%, p = .001; 3 months, 78.5% vs 72.1%, p = .02). For overall tumor response, ORRs 1 (p = .70) and 3 (p = .61) months after treatment were not significantly different between groups. Assessment of tumor response by mRECIST showed that the complete response rate based on local and overall tumor response at 1 month was significantly higher in the cTACE group than in the DEB-TACE group (local, 29.3% vs 20.8%, p = .003; overall, 21.2% vs 13.7%, p = .003) (Fig. S2). Results of subgroup analyses of treatment response based on BCLC stage are shown in Figures S3–S5. (Figs. S3–S5 can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708.) Subgroup analysis based on the size of DEBs (Fig. S6) showed no significant difference in outcomes between the 100- to 300-μm and 300- to 500-μm groups (all p > .05). (Fig. S6 can be viewed in the *AJR* electronic supplement to this article, available at doi.org/10.2214/AJR.20.24708.)

The two independent readers disagreed on the CT or MRI interpretation for treatment response in 6 of the 1002 patients (center A, two patients; center B, three patients; center C, one patient). These discrepancies were resolved by the third reader.

The mean α-fetoprotein level among all patients was 1197.9 ± 2188.3 ng/mL before TACE versus 855.5 ± 2099.5 ng/mL 1 month after TACE. The decrease in mean α-fetoprotein level was not significantly different between the DEB-TACE and cTACE groups (decrease of 420.1 ± 1340.1 ng/mL vs 296.7 ± 1855.4 ng/mL; p = .32).

Discussion

We comprehensively evaluated the safety and short-term efficacy of TACE to manage unresectable HCC in a multicenter sample of 1002 treatment-naive patients. Patients treated with DEB-TACE had more frequent liver or biliary injuries and locoregional hepatic complications and higher-grade abdominal pain than did patients treated with cTACE. The 3-month local tumor control rate was not significantly different between the two groups.

Dilated bile duct was the most common liver or biliary injury, having a frequency of 15.5% in the DEB-TACE group and 7.4% in cTACE group. These frequencies are comparable to those in a prior study [16] that included 151 patients with HCC in which the authors found biliary injuries at rates of 17.9% among patients undergoing DEB-TACE and 2.1% among those undergoing cTACE [16]. The observed higher frequency of portal vein narrowing in the DEB-TACE group than in the cTACE group in our study is also consistent with that in the earlier study, which showed frequencies of 7.1% and 1.4% [16]. In multivariable analysis, compared with cTACE, DEB-TACE had 2.3 times the odds [of being associated with a dilated bile duct. Kobayashi et al. [28] reported major histologic changes after TACE for HCC, including periductal fibrosis of bile ducts, bile duct epithelial injury and necrosis, and narrowing, stenosis, or thrombosis of the portal vein branch.

The bile ducts are supplied by the peribiliary plexus, which is supplied by hepatic arterial branches and can be damaged in hepatic arterial embolization [15]. In addition, doxorubicin-loaded beads can cause necrosis of surrounding normal liver tissue [29]. Furthermore, epirubicin, a semisynthetic derivative of doxorubicin, is associated with occlusion or stenosis of the hepatic artery [30]. Thus, the higher frequency of dilated bile duct in patients who undergo DEB injection may be due to ischemic bile duct damage caused by the bead agent, epirubicin, or both [16]. This may also account for the higher concentration of postprocedural total bilirubin in the DEB-TACE group. The observed portal vein narrowing may be due to compression or compromise of the surrounding portal vein branches by the exudate bile or fluid collection in the Glisson capsule [24]. The inflammatory process associated with the effects of DEBs and chemical arteritis may also cause portal vein narrowing [16, 24].

Patients with a noncirrhotic liver were at higher risk of liver abscess. The peribiliary plexus adjacent to the bile duct is preserved in cirrhosis. This preservation increases the risk of vascular collateralization after TACE, which could have lowered the risk of bile duct dilation in patients with cirrhosis [15]. Bile duct dilation is recognized to predispose to liver abscess [31]. It is possible that the vascular collateralization in livers with advanced cirrhosis prevents ischemic injury, thereby lowering the risk of abscess formation.

Abdominal pain was of higher grade in the DEB-TACE group, which differs from findings in the PRECISION V study [9] and the

PRECISION Italia Study Group trial [13]. The underlying physiopathology of post-TACE pain is not well understood. Acute ischemia of liver parenchyma, biliary ischemia, gallbladder ischemia, chemical injury to hepatic vessels, and transient swelling causing tension on the liver capsule are all potential causes [32, 33]. The higher grade of abdominal pain in the DEB-TACE group may be related to the higher frequency of bile duct dilation in this group. In addition, mean age was slightly higher in the DEB-TACE group, which might have also contributed to this group's greater susceptibility to pain [33].

Two prior prospective cohort studies [34, 35] showed a 1-month ORR of DEB-TACE of 60% and 71.4%, comparable to the 1-month ORR of 67.0% that we observed in the DEC-TACE group. In comparison, a more recent large prospective cohort study [8] showed an ORR of 83.6% within 1–3 months. That higher response rate may reflect different target populations; that study included patients with more advanced HCC. Theoretically, with more sustained and tumor-selective drug delivery and permanent embolization [19], DEB-TACE should afford better overall survival or tumor response than cTACE. Nevertheless, for short-term efficacy, we observed a better DCR for the overall tumor response in the cTACE group than in the DEB-TACE group at both 1-month and 3-month follow-up evaluations, consistent with results of a previous study [36]. The overall and local 1-month complete response rates were also significantly higher in the cTACE group than in the DEB-TACE group. A recent prospective randomized controlled trial [37] also showed significantly higher complete response rates for cTACE than for DEB-TACE 1 month (84.2% vs 35.7%,) and 3 months (75.2% vs 27.6%) after treatment.

This study had several limitations. First, its retrospective nature may have led to selection bias, and the cohort may not represent the broader population of patients with HCC. Patients in the DEB-TACE group were slightly older and had a higher proportion of advanced HCC. The indication for TACE itself in patients with advanced HCC is controversial because of the high risk of bile duct injury and hepatic infarction or hepatic failure in patients with advanced portal vein tumor thrombus. Patients with advanced HCC are more dependent on hepatic arterial supply and thus more susceptible to ischemic effects of TACE. The inclusion of such patients likely influenced the observed frequencies of bile duct dilation and portal vein narrowing and might have contributed to observed greater toxicity in the DEB-TACE group. In addition, treatment protocols varied in the cTACE group, as did the chemotherapeutic agents in both groups. The different protocols and agents might have had varying impact on efficacy and safety, including varying effect on the biliary tree. Although several agents (e.g., doxorubicin, epirubicin, and oxaliplatin) have been used for chemoembolization either as a sole agent or in a combination treatment regimen [38], no high-quality evidence indicates a best chemotherapeutic agent [39]. In addition, results of prior studies suggest that the choice of agent is not associated with biliary injury (e.g., biloma formation) [40, 41]. Other factors such as embolization level and the extent of embolization may also affect the frequency of bile duct or liver parenchymal ischemia. Finally, the enrolled patients underwent follow-up for a short period of 3 months. Treatment efficacy is better evaluated through median progression-free survival or overall survival. Further long-term efficacy assessment is ongoing.

In conclusion, this retrospective multicenter study showed that DEB-TACE is associated with more frequent locoregional hepatic toxicity and higher-grade abdominal pain than is cTACE in patients with unresectable HCC, though with similar 3-month local control rates. Greater caution and closer follow-up are therefore warranted for patients who undergo DEB-TACE for the treatment of unresectable HCC.

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(Editorial Comment starts on next page)

Editorial Comment: A Cautionary Experience With Drug-Eluting Bead Transarterial Chemoembolization for Hepatocellular Carcinoma

Worldwide, liver cancers are the fourth most common cause of cancer-related death [1]. Approximately 85% cases of hepatocellular carcinoma (HCC) are diagnosed at later stages, and underlying liver functionality limits treatment options. When transplant is not possible, many treatment modalities are available. Transarterial chemoembolization (TACE) is the standard approach to intermediate-stage HCC. Two randomized controlled trials and a meta-analysis have shown survival benefit of TACE compared with the best supportive care [2].

Drug-eluting bead TACE (DEB-TACE) is hypothesized to achieve higher tumor cytotoxicity with lower systemic effects than conventional TACE (cTACE). Evidence indicates that DEB-TACE has antitumoral activity similar to or perhaps even better than that of cTACE with fewer side effects. Not all studies have confirmed this view [3]. This controversy is further enhanced by the present investigation, a retrospective three-center study of cTACE versus DEB-TACE involving 1002 patients (most with hepatitis B) treated for HCC. The authors found significantly higher rates of liver changes (e.g., bile duct dilatation and portal vein narrowing) assessed 1 month after DEB-TACE than after cTACE. The rate of grade 3 abdominal pain was 6.1% for DEB-TACE versus 2.1% for cTACE. Other measures of postembolization syndrome were similar between groups.

The authors report similar rates of tumor control using modified RECIST, although a major study limitation is the short follow-up period of 3 months. The two study arms also used different agents: epirubicin (maximum 100 mg) for DEB-TACE versus doxorubicin (20–40 mg/m^2) and oxaliplatin (85 mg/m^2) with ethiodized oil (2–20 mL) for cTACE. Furthermore, portal vein invasion was more frequent at baseline in the DEB-TACE arm (p = .05). If longer follow-up periods prove the durability of the similar treatment effects between arms, then more caution and follow-up should be applied when using DEB-TACE for HCC control.

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