

Portal Vein Damage after DEB-TACE and Lipiodol-TACE: Based on Evaluation by Computed Tomography during Arterial Portography

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Abstract

Purpose: To reveal the effect of drug-eluting beads transarterial chemoembolization and Lipiodol transarterial chemoembolization on portal perfusion, and to identify factors predisposing portal vein damage after transarterial chemoembolization, based on evaluation by computed tomography during arterial portography.

Material and Methods: This retrospective cohort analysis included 49 patients with hepatocellular carcinoma who underwent transarterial chemoembolization and preprocedural/follow-up computed tomography during arterial portography between October 2013 and April 2015. The preprocedural and follow-up computed tomography during arterial portography were compared to identify the following new changes suggestive of portal vein damage in the follow-up computed tomography during arterial portography: small perfusion defects, large perfusion defects, and narrowing/disappearance or portal vein obstruction. The frequency of portal vein damage after drug-eluting beads transarterial chemoembolization and Lipiodol transarterial chemoembolization was calculated, and relationships between portal vein damage and clinical variables were analyzed. Finally, a multivariate logistic regression analysis with adjustments for potentially confounding factors was performed to identify factors predisposing portal vein damage.

Results: The analysis included 24 patients who underwent drug-eluting beads transarterial chemoembolization and 25 who underwent Lipiodol transarterial chemoembolization. Emergence of small perfusion defects and narrowing/disappearance or obstruction of portal vein were observed at a significantly higher frequency following drug-eluting beads transarterial chemoembolization than following Lipiodol transarterial chemoembolization (70.8% [17/24] vs. 20% [5/25]; $p < 0.001$; 41.7% [10/24] vs. 12% [3/25]; $p = 0.019$). Drug-eluting beads transarterial chemoembolization and selectivity of transarterial chemoembolization (selective [_{subsegmental}], segmental or lobar) were significantly associated with portal vein damage ($p < 0.001$ and $p = 0.016$, respectively). However, multivariate logistic regression analysis identified drug-eluting beads transarterial chemoembolization as a significant independent predictor of portal vein damage (odds ratio: 34.95; 95% confidence interval: 1.137-1073.99; $p = 0.042$).

Conclusions: Portal vein damage occurred at a significantly higher frequency following drug-eluting beads transarterial chemoembolization than following Lipiodol transarterial chemoembolization, and drug-eluting beads transarterial chemoembolization was an independent predictor of portal vein damage after transarterial chemoembolization.

Key words: Carcinoma, Hepatocellular, Chemoembolization, Therapeutic, Portal Vein, Multidetector Computed Tomography

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Introduction

Transarterial chemoembolization (TACE) is a widely adopted modality for treating hepatocellular carcinoma [1]. Conventional Lipiodol-TACE (LIP-TACE) has a long history and consists of injecting an emulsion composed of a chemotherapeutic agent, such as epirubicin, and iodized oil (Lipiodol), which is preferentially taken up by the tumor and serves as a local embolizing agent [2]. Recently-developed drug-eluting beads (DEB) offer simultaneous embolization and sustained release of the chemotherapeutic agent. DEB provides a far more favorable drug-release profile compared with drug/Lipiodol emulsions *in vitro* [3]. TACE also exposes the nontumoral liver parenchyma to a high concentration of chemotherapeutic agents for prolonged periods of time and ischemia, and sometimes causes portal vein damage (PVD), which has been reported as portal vein narrowing or portal vein obliteration after both LIP-TACE and DEB-TACE [4-7]. However, most studies have used only computed tomography (CT) or magnetic resonance imaging (MR) as the imaging modality for evaluation of the portal vein, and not CT during arterial portography (CTAP), which is considered as the most sensitive modality to evaluate portal vein and portal vein perfusion [8-11]. This study aimed to reveal the frequency of PVD after DEB-TACE compared with that after LIP-TACE and to identify factors predisposing PVD after TACE, based on evaluation by CTAP.

Materials and Methods

Populations

A total of 80 consecutive patients with hepatocellular carcinoma (HCC) who had undergone TACE and preprocedural/follow-up CTAP between October 2013 and April 2015 at Keio University and Hiratsuka City Hospital, were considered for inclusion in this retrospective cohort study. The institutional review board of the two hospitals approved the study protocol and waived written informed consent. The follow-up CTAP was performed primarily for the evaluation just before the subsequent TACE. Patients were excluded if they had undergone Balloon-occluded TACE (n = 1) or TACE using Cisplatin (n = 20), had not received treatment for intrahepatic lesions (n = 2), or had undergone ablation or surgery between the procedures (n = 8). The 1st TACE was included in the analysis if patients had undergone two or more sessions of TACE during this period. The study finally included 49 patients for analysis (age range: 60-87 years; mean age \pm standard deviation: 72.2 \pm 8.1 years).

Protocol for CTAP and CT during hepatic angiography (CTHA)

CTAP procedures were performed on an angio-CT system

(ACT FP 16, GE Healthcare at Keio University and INFX-8000C/Aquilion CXL, Canon Medical Systems at Hiratsuka City Hospital). For the CTAP procedure, 5 Fr. or 4 Fr. catheters were inserted via the femoral artery into the superior mesenteric artery. In the case of a replaced or accessory right hepatic artery, the catheter was inserted well beyond the origin of the hepatic artery to prevent contrast medium overflow into the hepatic artery. The patient received an injection 5 μ g of prostaglandin E1 into the superior mesenteric artery to increase the blood flow and decrease the laminar flow of the portal vein, double-phase CTAP scans were obtained 20 and 35 seconds after the start of infusion of 100 mL of 140 mg I/mL iohexol at the rate of 5 mL/second using a power injector at both hospitals. After the CTAP scans were obtained, 5 Fr. or 4 Fr. catheters or high-flow microcatheters were inserted into the common, right, and/or left hepatic artery for CTHA. Triple-phase CTHA scans were obtained 10, 22, and 34 seconds after 20 seconds of infusion of 140 mg I/mL iohexol at Keio University and 10, 24, and 28 seconds after 15 seconds of infusion of 140 mg I/mL iohexol at Hiratsuka City Hospital. The infusion rate was determined by digital subtraction angiography just before the CTHA at both hospitals. Both CTAP and CTHA images were evaluated for this study. At Keio University, the acquisition was performed under automatic exposure control (tube current modulation) with a noise index of 10 (thickness: 5 mm), and the tube current range ranged from a minimum of 100 mA to a maximum of 380 mA. The other scanning parameters were as follows: beam collimation of 10 mm, rotation time 0.5 second, pitch 1.375, table speed 13.75mm/rotation, and 120 kVp. At Hiratsuka City Hospital, the acquisition was performed under automatic exposure control (tube current modulation) with a noise index of 10 (thickness: 5mm), and the tube current range ranged from a minimum of 50 mA to a maximum of 450 mA. The other scanning parameters were as follows: beam collimation of 0.5 mm \times 64; rotation time, 0.5 second; pitch, 0.828; table speed, 21.8 mm/rotation; and 120 kVp.

TACE procedures

Board-certified interventional radiologists performed all TACE procedures. The patient was under conscious sedation through femoral access with a 5 Fr. or 4 Fr. catheter. After obtaining the CTAP images, selective catheterization of the proper hepatic artery was performed. When accessory hepatic arteries were present, they were catheterized successively. Digital subtraction angiography and CTHA were used to plan the arterial treatment and avoid embolic material injection into nonhepatic arteries. According to the site of involvement in the liver, selective catheterization of the artery feeding the tumors was performed. A microcatheter was used when needed. The choice of treatment (LIP-TACE or DEB-TACE) was left up to the discretion of the interventional radiologist. For LIP-TACE, a mixture of 50 mg of epirubicin, 5 mL of iodized oil (Lipiodol; Guerbet), and 5 mL of contrast medium was injected until adequate Lipiodol

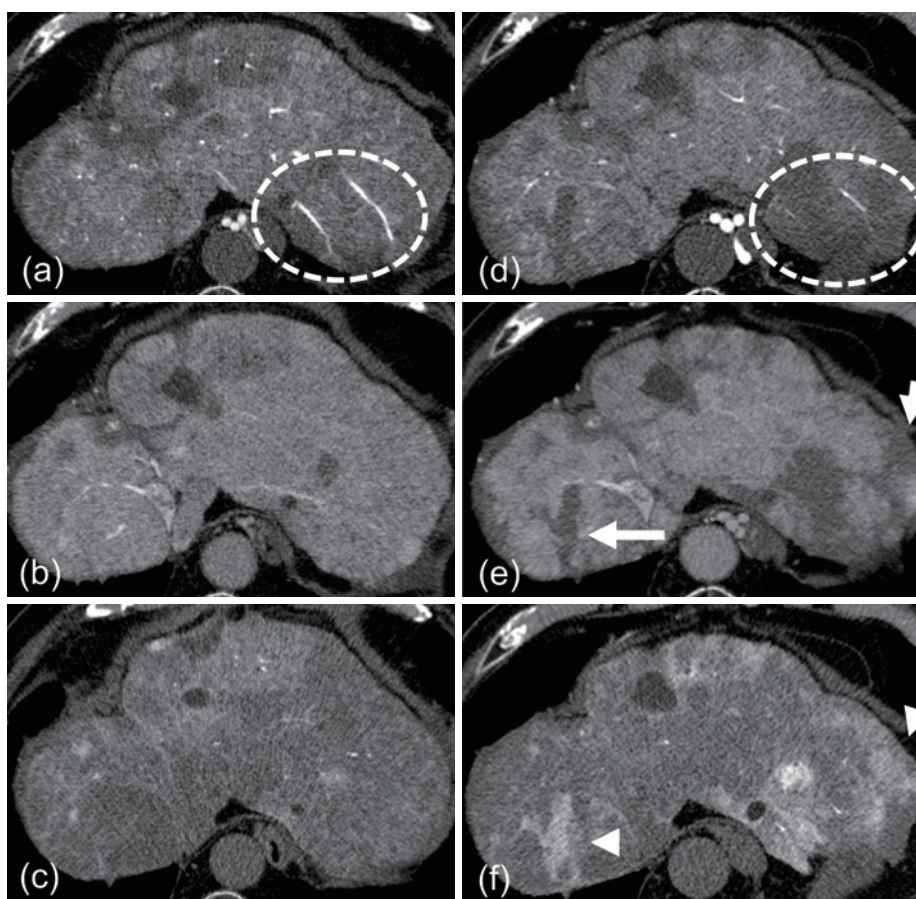


Figure 1. Example of small perfusion defects and narrowing/disappearance of the portal vein. Comparison of the preprocedural and follow-up CTHA/CTAP images in a 66-year-old male patient who underwent DEB-TACE.

(a) 1st phase of preprocedural CTAP; (b) 2nd phase of preprocedural CTAP; (c) 1st phase of preprocedural CTHA; (d) 1st phase of follow-up CTAP; (e) 2nd phase of follow-up CTAP; (f) 1st phase of follow-up CTHA.

The emergence of multiple small nontumorous perfusion defects on the CTAP images obtained after DEB-TACE (arrow) and the corresponding early and strong enhancement of the liver parenchyma on the CTHA images after DEB-TACE (arrowhead) were detected. Narrowing/disappearance of the peripheral portal vein branches was also observed (dotted circle). These findings indicate that the PVD caused by DEB-TACE leads to perfusion defects and corresponding-arterial-dominant, intense enhancement.

retention was achieved, followed by injection of a gelatin sponge (Gelpart 1 mm; Nippon Kayaku) until stasis was obtained. For DEB-TACE, 50 mg of epirubicin was loaded into one vial of DC-Beads (Eisai), each of which contained 2 mL of hydrated beads measuring 100-300 μm in diameter. When stasis failed to be obtained despite using an entire vial of DC-Beads or a vascular lake appeared [12], additional embolization with Embosphere (Nippon Kayaku) was performed at the end of the TACE session at the interventional radiologists' discretion.

Imaging analysis

The CTAP images were evaluated by consensus between two radiologists who were blinded to the clinical data (CT reader 1: an interventional and abdominal radiologist with 10 years of experience; CT reader 2: an interventional and

abdominal radiologist with 30 years of experience). The preprocedural and follow-up CTAP images were compared and the following new findings suggestive of PVD were checked for the area of embolization in the follow-up CTAP images (**Fig. 1** and **2**): small perfusion defects (smaller than a subsegmental area), large perfusion defects (equal to or larger than a subsegmental area), or narrowing/disappearance or obstruction of the portal vein. Narrowing was defined as a decreased diameter of the portal vein with preservation of the intraluminal blood flow, and disappearance or obstruction was defined as the absence of contrast enhancement of the corresponding portal vein [6]. By combined evaluation with the CTHA images, findings which were caused by tumor, portal vein tumor thrombus or obvious arteriportal shunt were excluded. Obvious arteriportal shunt was defined as the perfusion defects on CTAP accompanied by

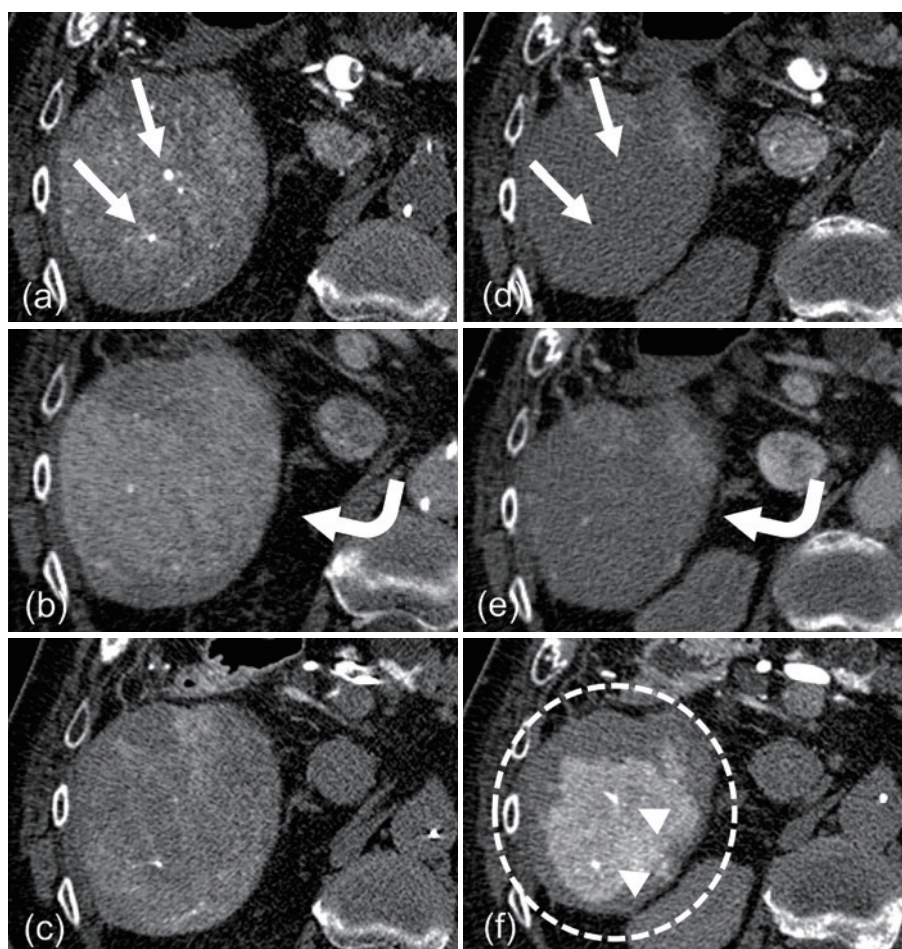


Figure 2. Example of large perfusion defect and disappearance/obstruction of portal vein. Comparison of the preprocedural and follow-up CTHA/CTAP images in a 66-year-old male patient who had undergone DEB-TACE.

(a) 1st phase of preprocedural CTAP; (b) 2nd phase of preprocedural CTAP; (c) 1st phase of preprocedural CTHA; (d) 1st phase of follow-up CTAP; (e) 2nd phase of follow-up CTAP; (f) 1st phase of follow-up CTHA.

After DEB-TACE, the CTAP images show the disappearance of a portal vein branch (arrow) and the emergence of a large perfusion defect (curved arrow). CTHA after DEB-TACE showed the corresponding stronger enhancement of the arterial branch (arrowhead) and liver parenchyma (dotted circle) on the CTHA images than that before DEB-TACE. Moreover, the volume of this segment became smaller, suggestive of atrophy. These findings indicate that obstruction of the portal vein branch caused by DEB-TACE led to the large perfusion defect and corresponding-arterial-dominant, intense enhancement.

corresponding early and strong enhancements with clear depiction of portal vein branch on CTHA.

Definitions

The following information was retrieved from the medical records: TACE type (DEB-TACE or LIP-TACE; because DEB has become available only since 2014 in Japan, our DEB-TACE group included only those patients who underwent DEB-TACE for the first time); the interval between the CTAPs (days); etiology of the underlying chronic liver dysfunction; Child-Pugh score and classification before TACE and after TACE (just before the follow-up CTAP); the number of previous treatments before TACE; number and maxi-

imum size of the tumors; whether the disease is bilobar or not; the selectivity of TACE (<subsegmental [selective], segmental, or lobar); and drug dose of epirubicin (mg).

Statistical analysis

Descriptive statistics for categorical variables were expressed as numbers or percentages and for continuous variables as mean \pm SD. First, the presence of a relationship between the TACE type and each variable, including PVD, was tested using the χ^2 test for categorical variables and the Mann-Whitney U test or the t-test for continuous variables. Then, the presence of a relationship between PVD and each variable was also tested using the χ^2 test for categorical

Table 1. Patient Characteristic of the Overall Subject Population, DEB-TACE Group, and LIP-TACE Group.

Group	Overall	DEB	LIP	P-value
Number of patients	49	24	25	
Age (years)	72.2 ± 8.1	71 ± 6.4	73.4 ± 9.4	0.189
Interval between CTAPs (days)	170.3 ± 79.1	131.9 ± 46.3	207.2 ± 86.3	0.001
Etiology				
CH-B	5 (10.2)	3 (12.5)	2 (8)	0.48
CH-C	26 (53.1)	10 (41.7)	16 (64)	0.117
NASH	4 (8.2)	1 (4.2)	3 (12)	0.32
ALC	14 (28.6)	10 (41.7)	4 (16)	0.047
PBC	1 (2.0)	0 (0)	1 (4)	0.543
N/A	2 (4.1)	1 (4.2)	1 (4)	0.745
CP score (before)	5.9 ± 0.87	6.0 ± 0.89	5.8 ± 0.85	0.523
CP classification (before)				
A	37 (75.5)	17 (70.8)	20 (80)	0.46
B	12 (24.5)	7 (29.2)	5 (20)	
C	0 (0)	0 (0)	0 (0)	
CP score (after)	6.0 ± 1.1	6.1 ± 1.2	5.8 ± 0.88	0.523
CP classification (after)				
A	37 (75.5)	18 (75)	19 (76)	0.872
B	11 (22.4)	5 (20.8)	6 (24)	
C	1 (2.0)	1 (4.2)	0 (0)	
Previous treatment (times)				
TACE	2.8 ± 3.1	3.6 ± 3.2	2.0 ± 2.8	0.057
Ablation	0.88 ± 1.3	1.0 ± 1.5	0.72 ± 1.1	0.53
Surgery	0.51 ± 0.76	0.63 ± 0.86	0.4 ± 0.63	0.4
Maximum size of the tumors (cm)	2.5 ± 0.16	2.3 ± 0.22	2.6 ± 0.22	0.265
≤3 cm	41 (83.7)	21 (87.5)	20 (80)	0.478
>3 cm	8 (16.3)	3 (12.5)	5 (20)	
Number of tumors	10.0 ± 2.2	13.7 ± 4.1	6.4 ± 1.4	0.015
≤3	18 (36.7)	4 (16.7)	14 (56)	0.004
≥4	31 (63.3)	20 (83.3)	11 (44)	
Bilobar disease	26 (53.1)	14 (58.3)	12 (48)	0.469
Selectivity				<0.001
lobar	24 (49.0)	21 (87.5)	3 (12.5)	<0.001
segmental	4 (8.2)	4 (16.7)	0 (0)	0.05
selective	21 (42.9)	0 (0)	21 (84)	<0.001
Amount of epirubicin (mg)	27.8 ± 12.6	29.8 ± 15.3	25.9 ± 9.0	0.389

TACE: Transcatheter arterial chemoembolization

DEB: Drug-eluting beads

LIP: Lipiodol

CTAP: CT during arterial portography

CH-B: Chronic hepatitis B

CH-C: Chronic hepatitis C

NASH: Non-alcoholic steatohepatitis

ALC: Alcoholic hepatitis

PBC: Primary biliary cholangitis

CP: Child-Pugh

variables and the Mann-Whitney U test or the t-test for continuous and ordinal variables. A probability value of <0.05 was considered statistically significant. To identify factors that could affect the likelihood of PVD after TACE, multivariate logistic regression with adjustments for confounding variables was performed to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs). Predictors identified through a univariate analysis were entered into the multivariate analysis model. Data were analyzed using commercially available statistical software (SPSS version 24, IBM SPSS, Armonk, New York).

Results

Table 1 summarizes the patients' characteristics. Among the 49 patients included, 24 had undergone DEB-TACE and 25 had undergone LIP-TACE. Compared with the LIP-TACE group, the DEB-TACE group included significantly higher numbers of patients with a shorter interval between the CTAPs, alcoholic hepatitis, a greater number of tumors, ≥4 tumors, and lobar TACE. In contrast, there was no significant difference in the Child-Pugh score or class before

Table 2. Frequency of Portal Vein Damage after TACE in the Overall Study Population, DEB-TACE Group, and LIP-TACE Group.

Group	Overall	DEB	LIP	P-value
Number of patients	49	24	25	
Small perfusion defect	22 (44.9)	17 (70.8)	5 (20)	<0.001
Large perfusion defect	4 (8.2)	4 (16.7)	0 (0)	0.05
Narrowing/disappearance or obstruction of PV	13 (26.5)	10 (41.7)	3 (12)	0.019

DEB: Drug-eluting beads

LIP: Lipiodol

PV: Portal vein

and after TACE or the amount of epirubicin administered between the DEB-TACE and LIP-TACE groups.

Table 2 summarizes the PVD findings. Small perfusion defects (**Fig. 1e**) and narrowing/disappearance or obstruction of the portal vein (**Fig. 1d**) were observed significantly more frequently in the DEB-TACE group ($p < 0.001$ and $p = 0.019$, respectively). There was also a strong tendency toward a higher frequency of large perfusion defects in the follow-up CTAP images in the DEB-TACE group (**Fig. 2d**). However, the difference was not statistically significant ($p = 0.05$). The perfusion defects were always accompanied by corresponding early and strong enhancements on CTHA (**Fig. 1f** and **2f**). These findings indicate that PVD caused by TACE leads to perfusion defects and the corresponding-arterial-dominant, intense enhancement. Small perfusion defects were observed in all the patients with large perfusion defects or narrowing/disappearance or obstruction of the portal vein, which might indicate that these findings could correlate with each other.

Table 3 presents the results of the univariate analysis performed to determine the relationship between PVD and each of the clinical variables. DEB-TACE and lobar TACE had been performed significantly more frequently in the patients in whom PVD was observed, whereas selective TACE was significantly less frequently performed in these patients. There were no significant differences in any of the other variables between the groups. According to these results, variables entered into the multivariate analysis model were DEB-TACE and selectivity of TACE. Multivariate logistic regression analysis identified only DEB-TACE as a significant independent predictor of PVD (OR 34.95; 95% CI 1.137-1073.99; $p = 0.042$).

Discussion

This study showed that PVD occurred at a significantly higher frequency after DEB-TACE than after LIP-TACE, based on evaluation by CTAP. In addition, only DEB-TACE was identified as an independent predictor of PVD after TACE. This result is important because our results showed a much higher frequency of PVD occurring after DEB-TACE than previous studies [6, 7]; this result could suggest unrecognized PVD after DEB-TACE.

According to the result of this study, DEB-TACE could

cause more frequent PVD compared with LIP-TACE. The cause of PVD after TACE is supposed to damage the peribiliary plexus, which is the primary feeder of the bile duct wall. This damage could be due to decreased arterial blood flow by embolization, the chemical insult of the vessel walls caused by the high concentration of chemotherapeutic agents, or both [6, 13]. This results in extravasation of bile or collection of reactive fluid in addition to bile duct dilatation along the sheaths of the Glisson capsule, which can gradually compress and compromise the adjacent portal vein branches [4]. A periportal inflammatory process related to the effect of high concentrations of chemotherapeutic agents administered to the periportal tissues, without direct extravasation of the bile, could also be involved in the PVD [14]. DEB-TACE offers simultaneous sustained drug release and embolization, which can provide higher concentrations of chemotherapeutic agents for more prolonged periods and a stronger embolization effect than that due to LIP-TACE. However, this favorable pharmacological advantage could increase the locoregional toxicity of DEB-TACE [3, 6, 7, 15, 16]. This supposition is consistent with our results, which showed DEB-TACE as an independent predictor of PVD after TACE.

Some recent studies have reported an association of DEB-TACE with PVD [6, 7]. Guiu et al. [6] showed that the frequency of portal vein narrowing and thrombosis after DEB-TACE for patients with HCC was higher than that after LIP-TACE, based on the findings of CT or MR (16.1% [9/56] vs. 2.8% [4/142] although the significance of the difference was not mentioned). In contrast, Monier et al. [7] reported that the frequency of portal vein thrombosis after DEB-TACE for patients with HCC was not significantly different from that after LIP-TACE, based on the findings of MR (4.4% [5/114] vs. 4.8% [8/116], $p = 0.62$). Compared with these previous reports, our results revealed a significantly higher frequency of PVD after DEB-TACE than that after LIP-TACE in our patients (70.8% vs. 20%; $p < 0.001$). This difference might occur because we used CTAP as the imaging modality for the evaluation, which is considered as the most sensitive modality to evaluate the hemodynamic change of the portal vein [8-11]. Our study could reveal unrecognized PVD after DEB-TACE, which might have been missed on CT or MR in previous studies.

This unrecognized PVD is an important factor that must

Table 3. Univariate Analysis Performed to Identify the Relationship between Portal Vein Damage and Each Variable.

Group	PVD (+)	PVD (-)	P-value
Number of patients	22	27	
Age (years)	72.7 ± 7.0	71.8 ± 9.0	0.817
Interval between two procedures (days)	163.3 ± 77.0	176.0 ± 80.4	0.673
DEB-TACE	17 (73.3)	7 (25.9)	<0.001
Etiology			
CH-B	1 (4.5)	4 (14.8)	0.245
CH-C	10 (45.5)	16 (59.3)	0.336
NASH	1 (4.5)	3 (11.1)	0.387
ALC	9 (40.9)	5 (18.5)	0.084
PBC	0 (0)	1 (3.7)	0.551
N/A	1 (4.5)	1 (3.7)	0.702
CP score (before)	5.9 ± 0.92	5.9 ± 0.83	0.831
CP classification (before)			
A	18 (81.8)	19 (70.4)	0.636
B	6 (27.3)	6 (22.2)	
C	0 (0)	0 (0)	
CP score (after)	5.9 ± 0.97	6.0 ± 1.1	0.616
CP classification (after)			
A	17 (77.3)	20 (74.1)	0.747
B	5 (22.7)	6 (22.2)	
C	0 (0)	1 (3.7)	
Previous treatment (times)			
TACE	3.2 ± 2.7	2.5 ± 3.4	0.106
Ablation	0.82 ± 1.2	0.93 ± 1.5	0.917
Surgery	0.59 ± 0.83	0.44 ± 0.68	0.573
Maximum size of the tumors (cm)	2.3 ± 0.21	2.6 ± 0.23	0.672
≤3 cm	19 (86.4)	22 (81.5)	0.476
>3 cm	3 (13.6)	5 (22.7)	
Number of tumors	8.3 ± 1.7	11.3 ± 3.7	0.709
≤3	6 (27.3)	12 (44.4)	0.215
≥4	16 (72.7)	15 (55.6)	
Bilobar disease	12 (54.5)	14 (51.9)	0.851
Selectivity			0.016
lobar	15 (68.2)	9 (33.3)	0.015
segmental	2 (9.1)	2 (7.4)	0.613
selective	5 (22.7)	16 (59.2)	0.01
Amount of epirubicin (mg)	28.6 ± 13.6	27.1 ± 11.7	0.683

TACE: Transcatheter arterial chemoembolization

PVD: Portal vein damage

DEB: Drug-eluting beads

CTAP: CT during arterial portography

CH-B: Chronic hepatitis B

CH-C: Chronic hepatitis C

NASH: Non-alcoholic steatohepatitis

ALC: Alcoholic hepatitis

PBC: Primary biliary cholangitis

CP: Child-Pugh

be checked before TACE, especially repetitive TACE. Joskin et al. [16] reported that pretreatment portal vein occlusion, even when localized, was a significant predictor of liver necrosis after TACE in NET patients. Moreover, they showed that in 41% (9 of 22) cases, biliary/portal damage linked to liver necrosis after subsequent TACE is itself induced by the previous TACE. Thus, they emphasized the importance of performing an imaging study before each TACE, even between two successive TACE sessions, to examine for biliary/portal damage, which must be considered even when localized. Although we completely agree with their opinion, PVD

after TACE could be missed or underestimated by CT or MR, as revealed by our present results. Repetitive TACE sessions after missing or underestimating PVD following a previous TACE could lead to progressive deterioration of the liver function and deterioration of the patients' prognoses. Thus, it is important to carefully check for PVD before each TACE session by CTAP using CT or cone-beam CT, especially after DEB-TACE, which our study showed was associated with a significantly higher frequency of PVD. Although no previous studies have shown the clinical significance of PVD found on CTAP just before TACE, the dis-

Table 4. Results of Multivariate Logistic Regression Analysis Performed to Identify Independent Predictors of Portal Vein Damage.

Risk factor	Portal Perfusion Damage			P-value
	OR	95% CI		
		Lower	Upper	
DEB	34.95	1.137	1073.99	0.042
Selectivity	0.468	0.081	2.71	0.397

OR: odds ratio

CI: Confidence interval

DEB: Drug-eluting beads

continuation of TACE could be considered, especially in the case of large perfusion defects or obstruction of the segmental portal vein.

The selectivity could also influence PVD incidence after TACE according to previous literature, but DEB-TACE might have a greater impact. Yu et al. [5] reported that selective treatment (segmental/subsegmental) induced more bile duct injuries as compared with more proximal (lobar/more proximal) drug delivery in a cohort of patients with hepatic malignancies (primarily HCC) treated by LIP-TACE. Although we performed selective TACE for most of the patients in the LIP-TACE group, there was a significantly lower number of patients with PVD in this group than in the DEB-TACE group, in which most patients had undergone nonselective lobar TACE. This finding would strengthen the idea that DEB-TACE is an independent risk factor for PVD or locoregional toxicities, even in cases undergoing less selective TACE, as verified by our study and previous studies [6, 7]. Therefore, we need to pay attention to this aspect in DEB-TACE because nonselective treatment exposes wider areas of the nontumoral liver to potential toxicities [7].

Our study had some limitations. First, we included only 49 patients and further studies with larger patient populations are warranted for confirming these preliminary findings. Second, our study was a retrospective study; hence, there is a possibility of selection bias. There were differences in the characteristics of tumor between the DEB-TACE and LIP-TACE groups. We selected the TACE type during the period included in this study primarily according to the results of the PRECISION V study [17], wherein DEB-TACE was more beneficial for patients with more advanced disease. Thus, our DEB-TACE group had a larger number of patients with multiple tumors, which might cause the confounding of DEB-TACE and selectivity of TACE because nonselective TACE tends to be performed for the patients with multiple tumors. In addition, the interval between the CTAP images was significantly longer in the patients of the LIP-TACE group, which might be due to the LIP-TACE including a smaller number of patients with multiple tumors. There is a possibility that these differences affected our results. However, the number of tumors and the interval be-

tween the CTAP imagings were not significantly associated with PVD risk in our study. Further prospective studies are warranted. Furthermore, the arterioportal shunt may sometimes be difficult to distinguish from small perfusion defects by PVD. Although these difficulties might have influenced the results of this study, previous literature suggests that arterioportal shunt could be caused by the chemical or ischemic injury of the portal vein after TACE [18], and thus the impact should be limited.

Final Conclusion

PVD was observed at a significantly higher frequency following DEB-TACE than following LIP-TACE, and DEB-TACE was identified as an independent predictor of PVD after TACE.

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References

1. Matsui O, Kadoya M, Yoshikawa J, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. *Radiology* 1993; 188: 79-83.
2. Boulin M, Schmitt A, Delhom E, et al. Improved stability of lipiodol-drug emulsion for transarterial chemoembolisation of hepatocellular carcinoma results in improved pharmacokinetic profile: proof of concept using idarubicin. *Eur Radiol* 2016; 26: 601-609.
3. Lewis AL, Taylor RR, Hall B, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. *J Vasc Interv Radiol* 2006; 17: 1335-1343.
4. Yu JS, Kim KW, Park MS, Yoon SW. Bile duct injuries leading to portal vein obliteration after transcatheter arterial chemoembolization in the liver: CT findings and initial observations. *Radiology* 2001; 221: 429-436.
5. Yu JS, Kim KW, Jeong MG, Lee DH, Park MS, Yoon SW. Predisposing factors of bile duct injury after transcatheter arterial chemoembolization (TACE) for hepatic malignancy. *Cardiovasc Intervent Radiol* 2002; 25: 270-274.
6. Guiu B, Deschamps F, Aho S, et al. Liver/biliary injuries following chemoembolisation of endocrine tumours and hepatocellular carcinoma: lipiodol vs. drug-eluting beads. *J Hepatol* 2012; 56: 609-617.
7. Monier A, Guiu B, Duran R, et al. Liver and biliary damages following transarterial chemoembolization of hepatocellular carcinoma: comparison between drug-eluting beads and lipiodol emulsion. *Eur Radiol* 2017; 27: 1431-1439.
8. Matsui O, Takashima T, Kadoya M. Dynamic computed tomography during arterial portography: the most sensitive examination for small hepatocellular carcinomas. *J Comput Assist Tomogr* 1985; 9: 19-24.
9. Tanaka Y, Sasaki Y, Katayama K, et al. Probability of hepatocellu-

- lar carcinoma of small hepatocellular nodules undetectable by computed tomography during arterial portography. *Hepatology* 2000; 31: 890-898.
10. Koizumi J, Kurata T, Yamashita T, et al. Computed tomography during arterial portography under temporary balloon occlusion of the hepatic artery: evaluation of pseudolesions caused by arterio-portal venous shunts. *Abdom Imaging* 2000; 25: 583-586
 11. Kudo M. Multistep human hepatocarcinogenesis: correlation of imaging with pathology. *J Gastroenterol* 2009; 44: 112-118.
 12. Seki A, Hori S, Shimono C. Management of vascular lake phenomenon on angiography during chemoembolization with superabsorbent polymer microspheres. *Jpn J Radiol* 2015; 33: 741-748.
 13. Kobayashi S, Nakanuma Y, Terada T, Matsui O. Postmortem survey of bile duct necrosis and biloma in hepatocellular carcinoma after transcatheter arterial chemoembolization therapy: relevance to microvascular damages of peribiliary capillary plexus. *Am J Gastroenterol* 1993; 88: 1410-1415.
 14. Shea WJ, Demas BE, Goldber HI, Hohn DC, Ferrell LD, Kerlan RK. Sclerosing cholangitis associated with hepatic arterial FUDR chemotherapy: radiographic-histologic correlation. *Am J Roentgenol* 1986; 146: 717-721.
 15. Namur J, Wassef M, Millot JM, Lewis AL, Manfait M, Laurent A. Drug-eluting beads for liver embolization: concentration of doxorubicin in tissue and in beads in a pig model. *J Vasc Interv Radiol* 2010; 21: 259-267.
 16. Joskin J, de Baere T, Auperin A, et al. Predisposing factors of liver necrosis after transcatheter arterial chemoembolization in liver metastases from neuroendocrine tumor. *Cardiovasc Intervent Radiol* 2014; 38: 372-380.
 17. Lammer J, Malagari K, Vogl T, 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.
 18. Chung J, Yu JS, Chung JJ, Kim JH, Kim KW. Haemodynamic events and localised parenchymal changes following transcatheter arterial chemoembolisation for hepatic malignancy: interpretation of imaging findings. *Br J Radiol* 2010; 83: 71-81.

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