Japanese Journal of Radiology (2019) 37:543–548
https://doi.org/10.1007/s11604-019-00840-4

ORIGINAL ARTICLE

Risk factors for local recurrence of hepatocellular carcinoma after transcatheter arterial chemoembolization with drug-eluting beads (DEB-TACE)

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Received: 2 November 2018 / Accepted: 18 April 2019 / Published online: 4 May 2019

Abstract

Purpose To identify the risk factors for local recurrence in hepatocellular carcinoma (HCC) patients treated with transcatheter arterial chemoembolization (TACE) with drug-eluting beads (DEB-TACE).

Materials and methods In this retrospective study, 35 patients (27 males, 8 females; median age 73 years) with 116 tumors (median size 14 mm) treated with DEB-TACE from May 2014 to September 2018 were evaluated. Age, sex, etiology, Child–Pugh class, alpha-fetoprotein, des-gamma-carboxyprothrombin, previous conventional TACE, tumor location, tumor size, tumor number, contact with the liver surface, level of embolization, corona enhancement on CT during hepatic arteriography, vascular lakes, additional embolization with gelatin sponge particles, and supplying vessels on digital subtraction angiography (DSA) after embolization were analyzed.

Results Univariate analysis showed that advanced age, female, large tumor, contact with the liver surface, and residual supplying vessels were significant risk factors for local recurrence ($p = 0.012$, 0.0013, 0.0023, 0.025, and < 0.001, respectively). On multivariate logistic analysis, large tumor, contact with the liver surface, and residual supplying vessels on DSA were significant risk factors for local recurrence ($p = 0.0026$, 0.038, and < 0.001, respectively).

Conclusion Large tumor size, contact with the liver surface, and residual supplying vessels on DSA were significant risk factors associated with local recurrence after DEB-TACE for HCC.

Keywords Hepatocellular carcinoma · Drug-eluting bead · DEB-TACE · Risk factor

Introduction

Transcatheter arterial chemoembolization (TACE) is the standard and effective therapy for intermediate hepatocellular carcinoma (HCC) [1–5]. Conventional TACE (cTACE) is a widely accepted technique using ethiodized oil (Lipiodol®, Guerbet Japan, Tokyo, Japan) and gelatin sponges. TACE with calibrated doxorubicin-carrying microspheres is a relatively new technique in recent decades. Use of drug-eluting beads (DEB) is a safe and effective procedure capable of ensuring highly sustained and tumor-selective drug delivery and permanent embolization [6, 7]. There have been some randomized, controlled trials and a meta-analysis comparing their efficiency and safety in the treatment of HCC patients [8–11]. These trials showed no significant differences in complete responses (CRs) and in the survival rate between cTACE and TACE with DEB (DEB-TACE).

Because the clinical results of these two methods for TACE are equivalent, there is currently no consensus regarding which method should be performed. As for cTACE, some risk factors for local recurrence have been demonstrated, such as the level of des-gamma-carboxyprothrombin (DCP), Lipiodol® uptake, multiple tumors, and large tumor size [12–14]. However, to the best of our knowledge, there

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has been only one report of predictive factors associated with local recurrence after DEB-TACE. Vesselle et al. reported the clinical and imaging features associated with CR after DEB-TACE; they found that tumor location in segments 1 and 4 was a negative factor for CR, and that tumor size < 5 cm was a positive factor [15]. Risk factors for local recurrence are little known. Thus, in the present study, the risk factors for local recurrence in HCC patients treated with DEB-TACE were investigated.

Materials and methods

Patients and tumors

This retrospective clinical study was approved by the Ethics Committee of our institution. Informed consent was obtained from all patients.

From May 2014 to September 2018, 58 consecutive patients with HCC who were treated with DEB-TACE using polyvinyl alcohol-based hydrogel particles (DC Bead ® 100–300 μm, Eisai, Tokyo, Japan) were evaluated. The exclusion criteria were: (1) HCCs with portal vein tumor thrombus (PVTT); (2) lost to follow-up; or (3) follow-up computed tomography (CT) not performed between 1 and 4 months after DEB-TACE. When the patient had 6 or more HCC nodules, the 5 largest nodules were chosen for evaluation. Finally, a total of 35 patients with 116 HCC nodules were enrolled (Fig. 1).

The patients' clinical characteristics are summarized in Table 1. All patients underwent pretreatment physical and laboratory examinations and CT during hepatic arteriography (CTHA). The median tumor diameter was 14 mm (range 3–120 mm).

Table 1 Demographic characteristics and pretreatment assessments of 35 patients who underwent DEB-TACE

Age (years)	73 (40–88)
Sex (male/female)	27/8
Etiology, HBV/HCV/AL/others	6/17/6/6
Child–Pugh class (A/B/C)	25/10/0
Albumin (g/dL)	3.8 (2.3–4.8)
Total bilirubin (mg/dL)	0.8 (0.3–2.8)
Prothrombin activity (%)	86 (46–120)
ALT (U/L)	35 (17–128)
AFP (ng/mL)	89.7 (2–29,157)
DCP (AU/L)	332 (11–22,847)
Number of previous cTACE	2 (0-6)
Number of tumors, 1/2/3/4/5/more	8/6/4/1/3/14

Data are median and range in age, albumin, total bilirubin, prothrombin activity, ALT, AFP and DCP, number of previous cTACE

DEB-TACE transcatheter arterial chemoembolization with drug-eluting beads, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AL* alcohol, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxyprothrombin, *cTACE* conventional TACE

DEB-TACE

Under local anesthesia, a 3 or 4 French sheath was inserted into the common femoral artery. Digital subtraction angiography (DSA) was performed with non-ionic iodine contrast (iohexol, Omnipaque® 300 iodine, 300 mg I/mL; Daiichi Sankyo, Tokyo, Japan). Then, CTHA or cone-beam computed tomography (CBCT) during hepatic arteriography (CBCTHA) was performed with an interventional radiology computed tomography (IVR-CT) system (Infinix/Activ, Toshiba Medical Systems, Tokyo, Japan) or with a C-Arm Dual-phase CBCT system (Artis zee BA Twin, Siemens

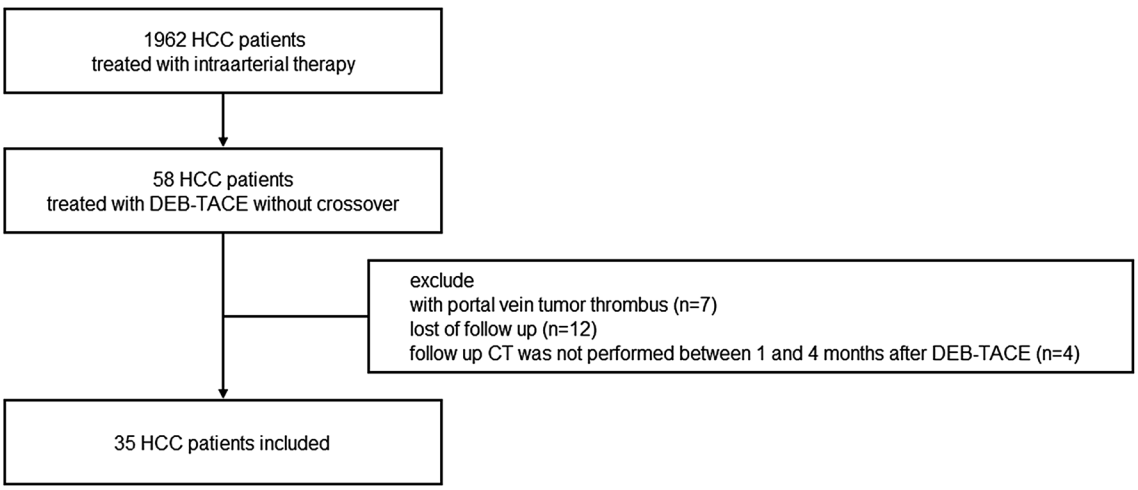

Fig. 1 Study flow chart

Healthcare GmbH, Forchheim, Germany). Twenty-two patients underwent CTHA and 13 patients underwent C-arm CBCTHA (Fig. 2).

DEB-TACE was conducted by injecting DC Bead® loaded with 50 mg of epirubicin (Epirubicin®, Nippon Kayaku, Tokyo, Japan) and diluted in 20 mL of contrast medium (Omnipaque® 300 iodine) into the tumor-supplying vessels. Embolization was terminated early in cases of sluggish flow. The injection was performed until tumor stain disappears on DSA. The maximum dose allowed per patient was two vials of DC Bead®. Additional bland embolization was performed with GS particles in 11 patients with 33 nodules because of intratumoral hemorrhage, so-called vascular lake, or remaining tumor stain on DSA after DEB-TACE.

Assessment of the CT and DSA findings and of the therapeutic effect

To assess of DEB-TACE treatment, early dynamic CT using 5-mm-thick slices was performed. Two experienced interventional radiologists (AY, MN) retrospectively reviewed the findings obtained by CTHA or CBCTHA and follow-up CT and DSA during DEB-TACE. They selected the five largest tumors in each patient, and they evaluated tumor location (segment 1 or 4, others), tumor size, tumor number, contact with the liver surface, and the level of embolization (lobar, subsegmental to segmental branch), presence of CTHA or CBCTHA corona enhancement [16, 17] (yes, no), vascular lake on DSA, and residual supplying vessel on DSA after embolization (appeared, disappeared). The presence or absence of treatment failure (the presence or absence of residual tumor stain on DSA after embolization) was evaluated. The observers discussed their decisions and reached a final decision by consensus in cases of discrepancies. Local recurrence was defined as the appearance of any enhancing tumors in a previously embolized area. The patients were followed-up every 1–4 months. The therapeutic effect was evaluated by dynamic CT 1–4 months after DEB-TACE.

Statistical analysis

Patient profile [age, sex, etiology (hepatitis C virus, others), Child–Pugh class (A, B), alpha-fetoprotein (AFP) ($<20, \geq 20$ ng/mL), DCP ($<40, \geq 40$ AU/L), history of previous cTACE (yes, no)], tumor characteristics [location of tumor (segment 1 or 4, others), tumor size, tumor number (single, multiple), contact with the liver surface (yes, no), CTHA (or CBCTHA) corona enhancement (yes, no)], and

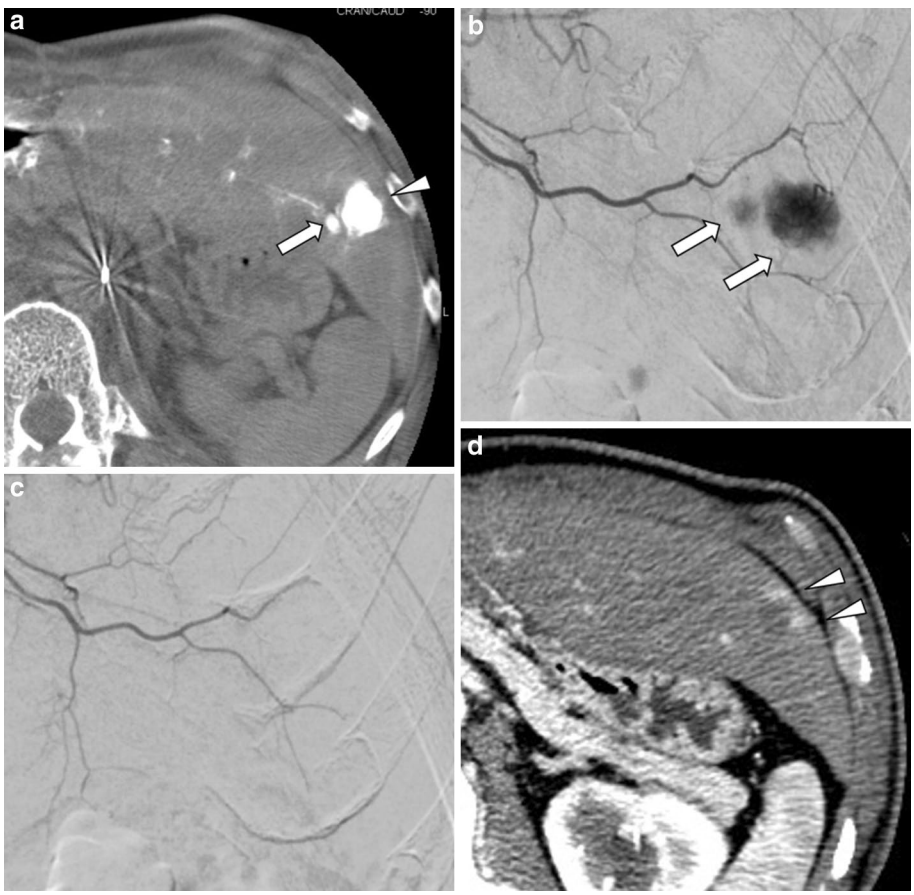

Fig. 2 A 61-year-old man with hepatocellular carcinoma in segment 3. **a** CT during hepatic arteriography shows hyper vascular hepatocellular carcinoma on the surface of segment 3. A satellite nodule is also visible (arrow) close to the main hepatocellular carcinoma (arrow head). **b** DSA in segment 3 shows tumor stain (arrow) of both tumors. **c** DSA in segment 3 after transcatheter arterial chemoembolization with drug-eluting beads shows disappearance of tumor stain. Note that the supplying vessel remains. **d** Arterial phase of dynamic CT 1 month after treatment shows recurrence on the surface of the liver. Note that the satellite nodule does not show any recurrence

procedure related factors [vascular lake (yes, no), level of embolization (lobar, subsegmental to segmental branch), additional embolization with GS particles (yes, no), and residual supplying vessel on DSA after embolization (appeared, disappeared)] were analyzed on univariate analysis and multivariate logistic regression analysis. Categorical variables were examined by Fisher's exact test. Continuous variables such as age, AFP, DCP, and tumor size were examined by Student's *t* test. The final multivariate logistic regression model for local recurrence was determined using the stepwise procedure. The results are shown as odds ratio with 95% confidence intervals (CIs). All statistical analyses were performed with JMP software (version 9.0.2, SAS Institute, Cary, NC, USA) for Microsoft Windows.

Results

DEB-TACE was performed successfully in all cases. There is no residual tumor stain on DSA after DEB-TACE.

Of the 116 nodules, 56 (48.3%) recurred 1–4 months after DEB-TACE. The results are shown in Table 2. The median follow-up time of CT evaluation was 1.6 months (1–4 months). On univariate analysis, age ($p = 0.012$), female ($p = 0.0013$), large tumor size ($p = 0.0023$), contact with the liver surface ($p = 0.025$), and appearance of residual supplying vessels on DSA after embolization ($p < 0.001$) had significant positive correlation with local recurrence (Table 2).

As shown in Table 3, multivariate logistic regression analysis showed that large tumor size ($p = 0.0026$), contact with the liver surface ($p = 0.038$), and the appearance of supplying vessels on DSA after embolization ($p < 0.001$) had significant positive correlation with local recurrence after DEB-TACE for HCC.

Discussion

This study showed that large tumor size, contact with the liver surface, and residual supplying vessels on DSA after embolization were significant risk factors for local recurrence after DEB-TACE for HCC. The PRECISION V study, a prospective randomized trial, found no significant differences in the effectiveness of the local control effect between DEB-TACE and cTACE [9]. Contact with the liver surface was not a risk factor in cTACE, while the presence of multiple tumors was not a risk factor in DEB-TACE [12–14]. In TACE for HCC, it would be necessary to select DEB-TACE or cTACE taking into account the patient's background and the size and location of the tumor, etc.

In this study, the number of previous cTACE procedures was not a significant risk factor for local recurrence of HCC

Table 2 Univariate analysis of risk factors for of local recurrence after DEB-TACE

	Therapeutic effect ($n = 116$)		*p* value
	No local recurrence ($n = 60$)	Local recurrence ($n = 56$)	
Age (years)			
Mean ± SD	66.6 ± 12.5	71.8 ± 9.4	0.012*
Sex			
Male	56	39	0.0013*
Female	4	17	
Etiology			
HCV	29	36	0.095
Others	31	20	
Child–Pugh class			
A	46	42	1
B	14	14	
AFP (ng/mL) $n = 111$			
< 20	26	19	0.33
≥ 20	31	35	
DCP (mAU/mL) $n = 98$			
< 40	13	9	0.47
≥ 40	37	39	
History of cTACE			
0	10	11	0.81
≥ 1	50	45	
Tumor location			
S1 or S4	7	15	0.057
Others	53	41	
Tumor size (mm)			
Mean ± SD	13.8 ± 6.0	22.3 ± 20.0	0.0023*
Tumor number			
Multiple	58	50	0.15
Single	2	6	
Contact with the liver surface			
Yes	23	34	0.025*
No	37	22	
Therapeutic vessel			
Segmental or subsegmental	11	19	0.060
Lobar	49	37	
Corona enhancement $n = 94$			
Yes	34	32	0.82
No	13	15	
Vascular lake			
Yes	6	8	0.57
No	54	48	
Additional GS			
Yes	19	14	0.54
No	41	42	
Supplying vessels			
Appear	13	37	< 0.001*
Disappear	47	19	

DEB-TACE transcatheter arterial chemoembolization with drug-eluting beads, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxyprothrombin, *cTACE* conventional TACE, *GS* gelatin sponge

Table 3 Multivariate logistic analysis

	Odds ratio	*p* value	CI 95%
Age	1.04	0.20	0.980–1.12
Sex (female)	2.51	0.34	0.432–20.8
AFP	1.00	0.083	0.999–1.00
Size	1.14	0.0026*	1.06–1.26
Multiple tumors	0.233	0.42	0.00551–10.3
History of cTACE	0.294	0.15	0.0504–1.53
Lober DEB-TACE	0.676	0.61	0.143–3.074
Contact with the liver surface	3.83	0.038*	1.14–14.9
Residual supplying vessel	22.7	< 0.001*	5.81–120
Tumor location (S1 or S4)	3.73	0.082	0.890–17.9

AFP alpha-fetoprotein, *cTACE* conventional transcatheter arterial chemoembolization, *DEB-TACE* transcatheter arterial chemoembolization with drug-eluting beads, *CI 95%* confidence intervals 95%

1–4 months after DEB-TACE. This can be interpreted as indicating that there was no significant difference in the local control effect, even if cTACE was performed before DEB-TACE. In contrast, arteries become narrowed or obstructed after cTACE [18, 19], and the incidence of recurrent liver cancer in patients who underwent cTACE more than twice was reported to be high [12]. DEB-TACE might be effective for the patients with the narrowed hepatic arteries.

Vesselle et al. and Kinugawa et al. reported that peripheral location of a tumor showed no significant correlation with local recurrence in their study of CR cases after DEB-TACE [15, 20]. However, HCC in contact with the liver surface was not studied. HCC in contact with the liver surface had a high local recurrence rate after DEB-TACE in this study. Involvement of an isolated artery may be possible reason for the high recurrence rate. The isolated artery is a part of the hepatic artery terminal branch and forms a microarterial plexus that is continuous with the hepatic capsular artery [21, 22]. This artery is associated with tumors in contact with the liver surface as supplying vessels [23]. The size of the DEB used in this study was 100–300 μm; thus, the DEB could not enter into microvessels, though Lipiodol® could [24]. This might be a reason why HCC in contact with the liver surface might be supplied from an isolated artery and survive.

Regarding the embolization endpoint in DEB-TACE, there is a report mentioning that the "contrast column should clear within 2–5 heartbeats" [25]. However, the PRECISION V randomized trial investigated a method in which embolization was carried out until stasis was achieved in the second or third branches [9], and Grosso et al. performed embolization until it was complete [26]. In the present study, the recurrence rate after DEB-TACE was significantly lower when the supplying vessels achieved complete stasis. Vesselle et al. [15] performed the procedure until the tumor stain disappeared and the nearby supplying vessels achieved stasis, and they reported the CR rate to be 36%, which was lower than the present rate (51.7%). It can be thought that the therapeutic effect will be better for lesions for which embolization is performed sufficiently to the point that DSA shows the supplying vessels to have disappeared.

Regarding tumor size, small HCCs had a low local recurrence rate after DEB-TACE. Past reports on HCC after cTACE include reports noting that size is a risk factor for recurrence [12, 14], as well as a report that it is not a significant risk factor when using a cutoff of 20 mm [20]. Regarding HCC after DEB-TACE, Vesselle et al. reported that a higher CR rate was significantly associated with small tumor size (< 5 cm), and that lesions of less than 2 cm had an even higher CR rate [15]. Taken together with the present result, both cTACE and DEB-TACE can be thought to achieve better local control in the case of smaller HCCs.

The present study has some limitations. First, this was a retrospective, single-arm study. Thus, it is difficult to compare to cTACE. Second, 1–5 large tumors per patient were analyzed, so there may have been sampling bias. Third, the follow-up period for evaluating the therapeutic effect and local recurrence was not constant, ranging from 1 to 4 months. Furthermore, in this article, the term "local recurrence" includes "residual tumor" because it is difficult to distinguish local recurrence from residual tumor.

In conclusion, this study showed that large tumor size, contact with the liver surface, and residual supplying vessels on DSA after embolization were significant risk factors associated with local recurrence after DEB-TACE for HCC.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent This is a retrospective study. For this type of study, formal consent is not required.

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