초기단계의 간세포암의 고식적 및 약물방출 경동맥화학색전술의 비교

이광훈 · 주승문 · 염태준 · 정상훈

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Conventional versus Drug-eluting Beads Trans-arterial Chemoembolization for Treatment of Hepatocellular Carcinoma at Very Early and Early Stages

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Background/Aims: To retrospectively compare conventional and drug-eluting beads trans-arterial chemoembolization (C-TACE and DEB-TACE) for treatment of hepatocellular carcinoma (HCC) at very early and early stages.

Methods: We retrospectively compared patients treated with C-TACE (n=115) or DEB-TACE (n=103) from September 2009 to May 2016. All patients were in a very early (stage 0) or early stage (stage A) of the Barcelona Clinic Liver Cancer (BCLC) staging system, and all had Child-Pugh class A and $\leq$ B7 liver status. Approval by the institutional review board was waived because the study was retrospective. The following parameters were evaluated: severe pain and bradycardia during TACE, post-embolization syndrome (PES), liver function change, complications, target tumor response, and conversion to another treatment modality. Numeric differences were assessed by the independent Student's t-test for continuous variables and by chi-square test for categorical variables.

Results: Severe intractable pain and bradycardia during the TACE procedure were significantly more frequent in the C-TACE group than in the DEB-TACE group ($P<0.001$). The incidence and duration of PES were significantly higher in the C-TACE group than in the DEB-TACE group ($P<0.001$). The increase in liver enzymes was significantly higher in the C-TACE group than in the DEB-TACE group ($P<0.001$). The deterioration of the Child-Pugh class was significantly higher in the C-TACE group than in the DEB-TACE group ($P=0.006$). There was no significant difference in serious complications except localized bile duct dilatation between the groups. There was no significant difference between the groups in tumor response at both immediate and 1-year assessment. The conversion rate to other treatment modalities was significantly higher in the DEB-TACE group than in the C-TACE group ($P<0.001$).

Conclusions: DEB-TACE is better than C-TACE in terms of procedural safety as initial treatment in a very early or early stage of HCC. (*J Liver Cancer* 2017;17:144-152)

Keywords: Hepatocellular carcinoma; Trans-arterial chemoembolization; Conventional; Drug-eluting beads

Received Jul. 29, 2017

Revised Aug. 23, 2017

Accepted Aug. 23, 2017

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INTRODUCTION

In the non-surgical treatment of hepatocellular carcinoma (HCC), conventional trans-arterial chemoembolization (C-TACE), which uses lipiodol as a drug vehicle to deliver anti-cancer agents, has been in use for over 40 years. In 2002, two randomized controlled clinical trials confirmed its value in standard palliative treatment of unresectable HCC,^{1,2} which was subsequently confirmed by the publication of two meta-analyses.^{3,4}

Drug-eluting beads trans-arterial chemoembolization (DEB-TACE) has been widely implemented in the West, replacing C-TACE, and has been recently implemented in Korea. The background of the DEB-TACE concept can be seen as a result of trying to improve the weaknesses of each of the components of C-TACE. First, the complex emulsion of lipiodol and anticancer agent used in C-TACE is not a true chemical bond; therefore, the components are separated within a short period of time, causing efflux of a large amount of anticancer drug into the systemic vein, and resulting in systemic side effects and deterioration of local anti-cancer effectiveness. Second, lipiodol itself is a very fine capillary level embolic droplet. In addition to inducing post-embolization syndrome (PES) in most patients, a lipiodol-anticancer emulsion stimulates micro-capillary damage to the peri-biliary plexus, resulting in irreversible complications such as progressive biliary injury, peri-biliary biloma, portal vein thrombosis, liver infarction, liver abscess, and even mortality from liver failure and sepsis.⁵ Third, in C-TACE, gelatin sponge particles or poly-vinyl alcohol particles are used as an embolization material to block the arterial blood flow. However, it is difficult to perform compact distal embolization because its shape is irregular and the size is not constant.

The use of drug-eluting beads aims to improve the drug-delivery system and the embolic material, which are the problems of C-TACE, while maintaining the basic principles of TACE. Theoretically, by controlling anti-cancer drug efflux to the whole body through reversible ionic-exchange of the cancer drug and the drug vehicle, and maximizing a constant concentration of the anti-cancer drug delivered to the inside of the HCC and periphery of tumor bed for a certain period,

DEB-TACE could become accepted for the treatment of HCC. Moreover, microspheres are a uniform shape and size and show a better distal compact embolic effect with DEB-TACE.^{6,7} However, microspheres as a drug carrier are a permanent embolic material. Therefore, the question arises regarding how many repeat procedures can be performed considering local tumor recurrence and frequent occurrence of HCC, especially in cases of very early small recurrence within a tight regular imaging follow-up. Because drug-eluting beads are larger than lipiodol, there is limited drug delivery and embolization to the portal vein side. In addition, since it uses a permanent embolic material, it can be difficult to apply DEB-TACE in a repeat second session of treatment.

It is clear that both C-TACE and DEB-TACE have their own advantages, and disadvantages or problems, and there are few large comparative papers on this subject, especially in the treatment of very early and early stages of HCC. Therefore, the purpose of this study is to compare these modalities as an initial treatment for HCC in a very early or early stage.

METHODS

We retrospectively analyzed and compared the use of C-TACE and DEB-TACE for the treatment of HCC from September 2009 to May 2016 using a controlled-match method.

Baseline characteristics of C-TACE and DEB-TACE groups are summarized in Table 1. There was no difference between the groups with regard to patient demographics, underlying liver disease, tumor staging, liver function, tumor size, and tumor markers.

All patients were in a very early (stage 0) or early stage (stage A) of the Barcelona Clinic Liver Cancer (BCLC) staging system.⁸⁻¹⁰ All patients had Child-Pugh class A or $\leq$ B7 liver status.

The inclusion criteria were follows: clinically or histologically diagnosed HCC according to the American Association for the Study of Liver Disease (AASLD) criteria,¹¹ no previous therapy, single HCC, Child-Pugh class $\leq$ B7, 1–5 cm maximum diameter and segmental involvement. Exclusion criteria were as follows: post-TACE follow-up period less than one year, Eastern Cooperative Oncology Group (ECOG) perfor-

mance status ≥ 1 , infiltrative/pedunculated/cirrhotosimetic morphology, bile duct invasion, vascular invasion, hepatofugal portal flow, total bilirubin ≥ 3 mg/dL.

Informed consent for TACE with both methods was obtained from all patients. Approval by the institutional review board was waived because the study was retrospective.

Before TACE, diagnostic angiography of the superior mesenteric artery and celiac trunk (or common hepatic artery) was performed using a 5-Fr angiographic catheter under local anesthesia via the common femoral artery approach to check for portal vein patency and maintained hepatopetal portal flow, to map hepatic arterial anatomy and to identify tumor feeding arteries of the HCC. In cases of multiple tumor feeding arteries, segmental arteries were selectively catheterized, whereas in smaller lesions with subsegmental tumor feeding artery, the subsegmental branch artery was superselected. Feeding arteries were selectively or superselectively catheterized using a microcatheter (2.0-Fr. Progreat[®] α , Terumo[®], Tokyo, Japan) with an appropriate microguide wire (0.016-inch Radiofocus[®] GT, Terumo[®], Tokyo, Japan; 0.016-inch Fathom[™], Heredia, Costa Rica). C-TACE (n=115) was performed using a mixture of lipiodol and doxorubicin (Adriamycin RDF; Ildong Pharmaceutical, Seoul, Korea), followed by embolization of the feeding artery using gelatin sponge particles. The maximum amount of lipiodol and doxorubicin was 10 mL and 50 mg, respectively. For DEB-TACE, two types of DEB were used, DC beads (Biocompatibles, Farnham, Surrey, UK; n=75), or Hepasphere (Biosphere Medical, Roissy, France; n=28) loaded with a maximum amount of 75 mg of doxorubicin per vial to 150 mg of doxorubicin loaded in two vials of DEB. For DC beads, in cases of small HCC with minimal vascularity, 100–300 μ m sized beads were chosen. If the HCC was large and vascularity was rich, we selected DC beads with a diameter of 300–500 μ m or a combination of both sizes of DC beads, i.e., 100–300 μ m sized beads first to embolize more distally, and then 300–500 μ m sized beads for proximal larger arteries. The hepasphere has a different mechanical property, it is a dry form, but become swollen in an aqueous condition, predictably by almost 4-fold in contrast media. For instance, 50–100 μ m hepasphere beads in dry form can expand to 200–400 μ m when hydrated in

contrast media. A 50–100 μ m sized dry form was used in this study, resulting in 200–400 μ m sized hydrated microspheres. The end point of C-TACE was the opacification of peritumoral portal veins by lipiodol and doxorubicin emulsion. The end point of DEB-TACE was defined as complete stasis of blood flow of the feeding artery for at least 10 seconds and no residual tumor staining from the target artery.

For comparison of the C-TACE and DEB-TACE methods, the following parameters were evaluated: severe pain and bradycardia during TACE, PES, changes in liver function, complications, target tumor response assessed by the European

Table 1. Baseline characteristics of C-TACE and DEB-TACE groups (no significant difference between groups)

	C-TACE	DEB-TACE
Number of patients	115	103
Sex (male, female), n (%)	92 (80):23 (20)	82 (79.6):21 (20.4)
Age, mean $\pm$ SD (range)	56.6 $\pm$ 6.3 years (40–81)	57.8 $\pm$ 5.5 years (43–75)
Liver disease, n (%)		
Hepatitis B	71/115 (61.7)	62/103 (60.2)
Hepatitis C	12/115 (10.4)	12/103 (11.7)
Non-B/Non-C	10/115 (8.7)	8/103 (7.8)
Alcoholic	22/115 (19.1)	21/103 (20.4)
BCLC stage, n (%)		
Very early stage (0)	34/115 (29.6)	28/103 (27.2)
Early stage (A)	81/115 (70.4)	75/103 (72.8)
Child-Pugh class, n (%)		
A	99/115 (86.1)	90/103 (87.4)
$\leq$ B7	16/115 (13.9)	13/103 (12.6)
Size of HCC, n (%)		
1–1.9 cm	33/115 (28.7)	28/103 (27.2)
2–2.9 cm	57/115 (49.6)	53/103 (51.5)
3–5 cm	25/115 (21.7)	22/103 (21.4)
Tumor marker, mean $\pm$ SD (range)		
α -FP, ng/mL	80 $\pm$ 192 (1–523)	87 $\pm$ 205 (1–586)
PIVKA-II, mAU/mL	36 $\pm$ 33 (0–98)	40 $\pm$ 38 (0–108)

C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization; BCLC, Barcelona clinic liver cancer; HCC, hepatocellular carcinoma; α -FP, alpha-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II.

Association for the Study of the Liver (EASL) criteria,¹²⁻¹⁵ and conversion to another treatment modality.

All patients were followed up with computed tomography (CT) or magnetic resonance imaging (MRI) within 1 month after TACE, and then at 3-month, 6-month and 1-year unless residual tumor or local tumor recurrence was evident.

Numeric differences between groups were assessed by the independent Student's *t* test for continuous variables and by chi-square test for categorical variables. The statistical results were considered to indicate significance if the *P*-value was less than 0.05.

RESULTS

1. Severe pain and bradycardia during TACE (Table 2)

The incidence of severe intractable pain during the TACE procedure was significantly higher in the C-TACE group (103/115 patients, 89.6%) than in the DEB-TACE group (12/103, 11.6%) (*P*<0.001). Most cases in the superselective C-TACE group required intravenous administration of the maximum dose of pethidine HCl (50 mg) and fentanyl citrate (100 µg). In cases of profound pain in the C-TACE group, bradycardia was accompanied in 30.4% of patients (*P*<0.001); in such cases, intravenous administration of atropine was mandatory. In all cases, the bradycardia-induced hypotension

recovered in a couple of minutes after intravenous administration of atropine.

2. PES (Table 3)

The incidence of PES was significantly higher in the C-TACE group than in the DEB-TACE group immediately after the procedure (*P*<0.001). Once there was improvement of the immediate PES symptoms and laboratory findings, the patient was discharged, and the duration of PES was determined at the 1-month out-patient visit. The duration of PES was also significantly longer in the C-TACE group than in the DEB-TACE group (*P*<0.001). A longer duration of PES was observed in cases with serious complications such as acute ischemic cholecystitis, liver parenchymal infarction, liver abscess, or biliary tree necrosis.

3. Changes in liver function (Table 4)

The immediate post-TACE increases in the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly higher in the C-TACE group than in the DEB-TACE group (*P*<0.001). In the C-TACE group, the mean±SD elevation of liver enzymes (AST and ALT) was 3.5±1.5-fold and 3.8±1.5-fold, respectively. In contrast, for DEB-TACE, the mean±SD elevation (AST and ALT) was 1.4±0.7-fold and 1.6±0.7-fold, respectively. Deteri-

Table 2. Severe pain and bradycardia during the TACE procedure

	C-TACE	DEB-TACE	<i>P</i> -value
Intractable pain	103/115 (89.6%)	12/103 (11.6%)	<0.001
Bradycardia*	35/115 (30.4%)	0/103 (0%)	<0.001

TACE, trans-arterial chemoembolization; C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization.

*Intravenous administration of atropine was mandatory in cases of bradycardia.

Table 3. Post-embolization syndrome (PES)

PES	C-TACE	DEB-TACE	<i>P</i> -value
Incidence	97/115 (84.4%)	29/103 (28.2%)	<0.001
Duration	3–31 days (mean, 9.36±6.71 days)	1–14 days (mean, 5.24±2.68 days)	<0.001

C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization.

oration of Child-Pugh class during the follow-up period was also significantly higher in the C-TACE group than in the DEB-TACE group ($P=0.006$). In the C-TACE group, worsening of Child-Pugh class occurred in 25.2% of patients, compared with 10.7% for DEB-TACE.

4. Serious complications (Table 5)

There was no significant difference in the incidence of serious complications except localized bile duct dilatation between the groups. Rare (<1%) ischemic cholecystitis occurred in one patient in each group, probably due to regurgitation of the chemoemulsion and embolic materials. The patient who underwent C-TACE was treated conservatively and recovered from cholecystitis. The patient who underwent DEB-TACE was treated by percutaneous cholecystostomy and recovered. Peri-tumoral parenchymal ischemic changes, other than overt infarction, were observed in about 20% of patients in both groups at the first follow-up imaging without any clinical significance. Overt liver infarction around the tumor bed occurred in about 3% of each group, and was managed conser-

vatively without any intervention. Liver abscess formation in infarcted tumor and the surrounding liver parenchyma occurred in one patient in each group, and was treated by percutaneous tube drainage and intravenous antibiotics. A higher rate of localized bile duct dilatation was evident in the DEB-TACE group (29/103, 28.2%) compared with the C-TACE group (7/115, 6.1%) ($P<0.001$) during the follow-up imaging, but there were no clinical sequelae. Two patients in the C-TACE group experienced progressive extensive whole biliary tree necrosis that resulted in liver failure and mortality. One patient in the DEB-TACE group experienced biliary tree necrosis, but it was confined to a unilobar affected site without progression. One mortality in the DEB-TACE group was due to subsequent radiofrequency ablation (RFA) conversion for the treatment of the residual viable portion after the initial DEB-TACE; extensive portal vein thrombosis after the RFA resulted in liver failure and mortality.

5. Target tumor response (Table 6)

The rates of target tumor response assessed by EASL crite-

Table 4. Change in liver function

Liver function change	C-TACE	DEB-TACE	P-value
AST/ALT elevation	3.5±1.5/3.8±1.5 folds	1.4±0.7/1.6±0.7 folds	<0.001
Child-Pugh class change	25.2% deterioration	10.7% deterioration	0.006

AST, aspartate aminotransferase; ALT, alanine aminotransferase; C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization.

Table 5. Serious complications

Serious complications	C-TACE	DEB-TACE	P-value
Acute cholecystitis	1/115 (0.9%)	1/103 (0.97%)	NS
Peri-tumoral parenchymal ischemia	23/115 (20%)	21/103 (20.4%)	NS
Liver infarction	3/115 (2.6%)	3/103 (2.9%)	NS
Liver abscess	1/115 (0.9%)	1/103 (0.97%)	NS
Localized bile duct dilatation	7/115 (6.1%)	29/103 (28.2%)	<0.001
Biliary tree necrosis	2/115 (1.7%)	1/103 (0.97%)	0.333
Liver failure	2/115 (1.7%)	1/103 (0.97%)	NS
Mortality*	2/115 (1.7%)	1/103 (0.97%)	NS

C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization; NS, not significant.

*Two mortalities in the C-TACE group were from extensive biliary necrosis resulting in liver failure, one mortality in the DEB-TACE group was due to subsequent conversion to radiofrequency ablation (RFA) for the treatment of residual viable portion.

Table 6. Target tumor response assessed by European Association for the Study of the Liver (EASL) criteria

Tumor response	C-TACE (%)		DEB-TACE (%)		P-value	
	Immediate	1-year	Immediate	1-year	Immediate	1-year
Complete response	81.7	79.6	77.7	77.5	0.455	0.695
Partial response	13	5.3	18.4	3.9	0.272	0.629
Objective response	94.8	85	96.1	81.4	0.638	0.482
Stable disease	0	5.3	0	6.9	NA	0.633
Progressive disease	5.2	9.7	3.9	11.8	0.638	0.631

C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization; NA, not available.

Table 7. Conversion to another treatment modality

	C-TACE	DEB-TACE	P-value
Conversion to another modality	10/115 (8.7%)	35/103 (40%)	<0.001

C-TACE, conventional-trans-arterial chemoembolization; DEB-TACE, drug-eluting beads-trans-arterial chemoembolization.

ria are summarized in Table 6. By the definition of all responses, there was no significant difference between the two modalities as an initial treatment choice at both the immediate and 1-year assessment. Immediate complete response rates in C-TACE and DEB-TACE groups were 81.7% and 77.7%, respectively. Immediate objective response rates in C-TACE and DEB-TACE groups were 94.8% and 96.1%, respectively. One-year objective response rates in C-TACE and DEB-TACE groups were 85% and 81.4%, respectively. Similar rates of stable disease and progressive disease between the groups were observed at the 1-year follow up.

6. Conversion to other treatment modalities (Table 7)

At the study end time of 1-year, the conversion rate to other treatment modalities such as surgical resection, RFA, or exchange between C-TACE and DEB-TACE was significantly higher in the DEB-TACE group (35/103, 40%) than in the C-TACE group (10/115, 8.7%) ($P<0.001$).

DISCUSSION

DEB-TACE has been reported to have a more stable phar-

macokinetics profile than C-TACE in both animal and clinical trials.^{6,7,16,17} An earlier trial comparing C-TACE and DEB-TACE showed that complications associated with the procedure and the effusion of anticancer drugs and hepatic dysfunction were less likely to occur in the DEB-TACE group. In addition, the objective response rate and disease control rate of HCC were found to be better in the DEB-TACE group.¹⁸ However, this was an early result of 6 months, and no additional results have been reported since then. In an earlier meta-analysis including a total of seven clinical studies with 700 patients, DEB-TACE showed a significantly better tumor response compared with C-TACE and better survival for 1 and 2 years, in addition to a safer profile than C-TACE.¹⁹ In addition, in a more recent meta-analysis of nine clinical studies with 866 patients, DEB-TACE also showed a higher complete response rate and a higher overall survival rate as well as a safer profile and fewer adverse events than C-TACE.²⁰

However, a couple of recent studies suggested different conclusions. A systematic review that included four randomized controlled trials, one uncontrolled prospective study and one prospective case-control study, with a total of 652 patients, suggested that DEB-TACE was associated with better tumor response and potentially fewer adverse events, but there was no survival benefit compared with C-TACE.²¹ Although it was retrospective, a recent study that compared the clinical outcomes of 250 patients (C-TACE, $n=144$; DEB-TACE, $n=106$) in terms of overall survival and time to progression showed no significant difference in the median overall survival (44.9 months in C-TACE group, 46.6 months in DEB-TACE group), but a significantly longer median time to

progression in the C-TACE group (13.3 months) compared with the DEB-TACE group (10.8 months). The authors concluded that DEB-TACE appeared to be safer, but was not superior to C-TACE with regard to clinical efficacy.²²

Thus, the factors to consider when comparing C-TACE and DEB-TACE are both procedural safety and clinical outcome. Currently, procedural safety and patient compliance are clearly better for DEB-TACE than C-TACE, but clinical outcome remains controversial.²¹⁻²⁵

For safety issues such as severe intractable pain and bradycardia during the procedure, PES, liver function changes, and severe complications, we believe that the difference arises from the basic different characteristics of the chemo-vehicles and embolic materials of C-TACE and DEB-TACE. In C-TACE, severe ischemic pain occurs during the procedure because of irritation to the peri-biliary plexus and liver capsule due to the smaller chemo-laden lipiodol droplets, which are an emulsion of the anticancer agent and lipiodol. In some cases, blood pressure control and treatment of bradycardia are required. In the case of DEB-TACE, pain is relatively rare and tends to be vague and tolerable, and the vital signs remain stable during the procedure. Basically, both C-TACE and DEB-TACE are embolic procedures that cause deterioration of liver function and PES. However, most of the reports and meta-analyses have shown significantly higher fluctuations in the liver function profiles and incidence of PES with C-TACE compared to DEB-TACE. This result correlates with preclinical studies of the pharmacokinetics profiles.^{6,7} A recent report of a Korean multicenter registry of DEB-TACE using DC beads presented a high rate of PES (73%) after the first treatment cycle.²⁶ The low incidence of PES in the DEB-TACE group in the current study might be due to the small to medium sized single HCC cohort with a small extent of involved liver. One report comparing the short-term safety and efficacy of DEB-TACE and C-TACE using the superselective TACE method showed no difference in overall toxicity between the two groups.²⁷ The authors explained that the reason for this might be the superselective procedure. In our study, we found significantly higher incidence of severe pain and bradycardia, changes in liver enzymes, and PES in the C-TACE group than in the DEB-TACE group. This difference is

probably because the chemo-lipiodol emulsion sufficiently effluxes into the surrounding peri-tumoral portal venous system when superselective TACE is performed. The most serious complication of TACE is profound tumor and liver infarction resulting in abscess formation and biliary tree necrosis. An abscess can be managed by percutaneous drainage, but extensive biliary tree necrosis might result in liver failure and mortality. Biliary tree necrosis in C-TACE can be progressive, whereas most of the bile duct injury in DEB-TACE is localized without clinical sequelae. This can be explained by the fact that the smaller sized chemo-lipiodol emulsion can be delivered to a fine peribiliary plexus, resulting in progressive damage, but this is unlikely to occur with the larger sized DEB microspheres. The reason why localized bilateral duct dilatation occurs more frequently in DEB-TACE than C-TACE is probably that DEB-TACE has a stronger embolic effect and therefore a profound liver parenchymal ischemic volume change occurs in the tumor bed. However, peribiliary plexus injury is unlikely to be severe in DEB-TACE, as it is no longer progression. Progressive biliary necrosis is thought to be more at risk in C-TACE. Because drug-laden lipiodol is very small size, peribiliary plexus injury can be induced, but DEB of more than 100 μm is less likely to induce peribiliary plexus injury. One progressive biliary necrosis occurred in the DEB-TACE group, not after DEB-TACE, but after RFA for residual viable portion.

Regarding clinical outcome, it is hard to compare the data since most of the patients were converted to other treatment modalities during the follow-up based on institutional policy or the individual clinician's preference if there was any local tumor recurrence, even with a very small viable portion. By the end point, conversion to other therapies such as surgery, RFA, adjunctive external beam radiation therapy, conversion from DEB-TACE to C-TACE, and systemic chemotherapy or molecular targeting agent occurred upon recurrence in almost all patients. C-TACE can be performed as many times as needed because of the small size of the chemo-lipiodol emulsion, which can be delivered even to fine collaterals or injured arteries. If local recurrence occurs again to less effectiveness C-TACE through such collaterals or injured arteries, then conversion to other therapies such as surgery or RFA

should be decided. In contrast, for DEB-TACE, there is an apparent limitation of repeat procedures. Since DEB microspheres are permanent embolic materials, there is deprivation of the native arteries and fine collateral formation; therefore, large DEB microspheres cannot be delivered to fine collaterals or damaged arteries. Such cases should be converted to C-TACE or RFA. For this reason, even when the initial treatment is started with DEB-TACE, it is difficult to compare the true clinical outcomes for the two modalities because the same treatment is often not continued.

A limitation of this study is that it is a retrospective case-controlled observation with immediate and early-term data at 1 year. Also, as mentioned above, the true clinical outcomes could not be presented.

In conclusion, DEB-TACE is certainly better than C-TACE in terms of procedural safety as initial treatment in a very early or early stage of HCC. However, a true comparative long-term study of the differences between the two modalities for tumor control and clinical outcome appears to be difficult. Because the morphological classifications of HCC and clinical liver function status are very diverse, it is advisable to know the advantages and limitations of both C-TACE and DEB-TACE and to choose the appropriate treatment method for each patient or even for the same patient during the course of treatment.

FUNDING

The Scientific Research Fund of the Korean Liver Cancer Study Group 2015

AUTHOR CONTRIBUTIONS

Kwang-Hun Lee, primary procedure operator, manuscript writing; Seung-Moon Joo, primary procedure operator; Tae Jun Yum, secondary procedure operator, statistic analysis; Sang Hoon Jung, secondary procedure operator, data collection.

Conflicts of Interest

The authors have no conflicts to disclose.

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