



Original Article

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Transarterial chemoembolization using drug-eluting bead compared with radiofrequency ablation for treatment of single small hepatocellular carcinoma: a pilot non-randomized trial

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Background/Aims: Surgical resection, transplantation, and radiofrequency ablation (RFA) are generally accepted as amenable treatments for small hepatocellular carcinoma (HCC). Recently drug-eluting beads (DEB) which had several treatment advantages were introduced for transarterial chemoembolization (TACE). The aim of this study was to evaluate feasibility and safety of DEB-TACE compared with RFA for the treatment of single small HCC.

Methods: In this pilot non-randomized trial, we assessed retrospective data of 40 patients who underwent DEB-TACE (n=21) or RFA (n=19) for single small (≤ 3 centimeter in greatest dimension) HCC. The primary outcomes were tumor response and time to recurrence. The secondary outcome was treatment-related complications.

Results: Complete response rate to DEB-TACE and RFA after first follow-up assessment was 90.5% and 94.7%, respectively ($P=1.000$). During mean follow-up of 87.6 months (95% confidence interval, 74.4-102), 7 patients experienced local recurrence. The 6- and 12-month cumulative local recurrence rate was 5.0% and 21.8% in DEB-TACE vs. 11.1% and 17.0% in RFA group ($P=0.877$). A total 14 distant intrahepatic recurrences were developed and 12- and 24-month cumulative distant intrahepatic recurrence rate was 20.6% and 42.7% in DEB-TACE vs. 17.2% and 36.3% in RFA group ($P=0.844$). Two patients experienced gangrenous cholecystitis after DEB-TACE requiring cholecystectomy as treatment-related adverse event.

Conclusions: Tumor response and recurrence rate after single session of DEB-TACE or RFA were similar. DEB-TACE could be applied selectively in patients with a single small HCC if the other therapeutic modality is unfeasible. (*J Liver Cancer* 2021;21:146-154)

Keywords: Hepatocellular carcinoma; Radiofrequency ablation; Recurrence; Transarterial chemoembolization

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INTRODUCTION

Among primary liver malignancies, hepatocellular carcinoma (HCC) represents the major histological subtype accounting for 70% to 85% of the total liver cancer burden

worldwide.¹ Although the mainstays of therapy for small HCC are surgical resection and liver transplantation, many HCC patients are not eligible for surgery because of underlying liver dysfunction or organ shortage. Other accepted interventional treatments including radiofrequency ablation (RFA) and percutaneous ethanol injection have been used to treat small HCC based on institutional preference, but a technical difficulty of local treatments may be encountered particularly when tumor is centrally located or adjacent to large vessels, gallbladder or intestine.

Transarterial chemoembolization (TACE) is commonly used for unresectable or multifocal HCCs that are not amenable to other local treatments.^{2,3} While embolization induces tumor ischemia by disrupting the blood supply to the tumor, its combination with chemotherapeutic agents results in a strong cytotoxic effect.^{4,5} Recently, drug-eluting beads (DEB) which had the ability to sequester chemotherapeutic agent from solution and release it in a sustained and controlled mode were introduced for TACE.⁶ The purpose of this study was to evaluate feasibility and safety of DEB-TACE compared with RFA for the treatment of a single small HCC.

METHODS

1. Ethics statement

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board (IRB no. 2020-L09-01). The requirement for informed consent from patients was waived due to the retrospective nature of this study.

2. Patients

This is a pilot non-randomized trial through a retrospective chart review in a single center. Consecutive patients who underwent at least one session of DEB-TACE or RFA for first treatment of single small HCC from October 2010 to March 2017 and who met the following eligibility criteria were included. Eligibility criteria were as follows: 1) newly diagnosed, treatment-naïve HCC, 2) Child-Pugh class A or B, 3) Eastern Cooperative Oncology Group (ECOG) perfor-

mance status 0, 1 or 2, and 4) absence of main portal vein thrombosis and extrahepatic metastases.⁷ Patients at high risk for surgery or those who were unwilling to receive operation in spite of the clinician's advice were included. We excluded patients with previous histories of intra- or extrahepatic malignancies (n=3), poor hepatic reservoir function of Child-Pugh class C (n=11), medically uncontrolled or recurrent hepatic encephalopathy (n=4), and poor performance status of ECOG 3 or higher (n=7). As a result, a total of 40 patients were finally included in this study. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines were followed (Supplementary Table 1).

3. Diagnosis of HCC

Diagnosis of a small (≤ 3 cm in greatest dimension) solitary HCC was made based upon the typical radiological findings (arterial hypervascularity and venous/late phase washout) on dynamic computed tomography (CT). In all patients, a radiological diagnosis of HCC was ascertained by gadoxetic acid (Primovist[®], Bayer HealthCare, Leverkusen, Germany)-enhanced magnetic resonance imaging (MRI) following dynamic CT.^{8,9} On gadoxetic acid-enhanced MRI, lesions satisfying at least two findings within the following criteria were considered as HCC nodules: 1) arterial enhancement with or without portal/equilibrium phase washout, 2) hypointensity on hepatobiliary phase, 3) hyperintensity on T2-weighted image, and 4) hyperintensity on diffusion-weighted image.¹⁰

4. TACE protocol

One radiologist with 25 years of experience in intervention performed all procedures. After hepatic and superior mesenteric artery angiography to check for arteriovenous shunts, and identification of arterial tumor supply, feeding arteries were selectively catheterized using a microcatheter. After positioning the microcatheter tip close to the tumor-feeding branch, a mixture of 1 vial of DEB (70-150 or 100-300 μ m diameter; DC Bead[®], Biocompatibles, Farnham, UK) loaded with doxorubicin (50 or 75 mg) and contrast agent was infused until the flow through the tumor-feeding artery was slowed down.

5. RFA protocol

Under conscious sedation and local anesthesia, all RFA procedures were performed percutaneously by the aforementioned radiologist. LeVein needle electrode[®] (Boston Scientific, Marlborough, MA, USA) or Well-Point RF electrode[®] (STARmed, Goyang, Korea) were used according to the manufacturers' recommended protocols. Real-time sonographic guidance and monitoring was made for adequate ablation during procedure. In case of invisible HCC at sonographic targeting, CT was applied for adequate needle positioning prior to and post-ablation.

6. Radiological follow-up and treatment response

Primary outcomes were tumor response and local and distant intrahepatic recurrences of HCC. Local recurrence of HCC was defined when enhancing tumor reemerged at the target lesion and distant intrahepatic recurrence was defined when the new HCC was developed at a separate intrahepatic

site.¹¹ These were evaluated by regular follow-up with CT scan and/or MRI at 1, 3, and 5-6 months after receiving DEB-TACE or RFA, using the modified Response Evaluation Criteria in Solid Tumors.¹² Complete response was defined as disappearance of intratumoral enhancement; partial response was defined as a $\geq 30\%$ decrease in the sum of the diameters of viable lesion; progressive disease was defined as an increase of $\geq 20\%$ in the sum of diameters of viable tumor; and stable disease was defined as any cases that did not qualify as either partial response or progressive disease. Patients who were diagnosed with HCC recurrence after initial treatment were assigned to sequential therapeutic modalities.

7. Safety

The secondary endpoint was treatment-related complication. Laboratory tests were performed 1, 3-7, 14 days and every 4-12 weeks after treatment. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (version 4.0).¹³

Table 1. Baseline characteristics of the patients (DEB-TACE group vs. RFA group)

Variable	DEB-TACE group (n=21)	RFA group (n=19)	P-value*
Age (years)	65 (43-84)	69 (47-76)	0.978
Sex (male)	12 (57.1)	15 (78.9)	0.186
ECOG performance status (grade 0/1/2)	13/5/3 (61.9/23.8/14.3)	11/6/2 (57.9/31.6/10.5)	0.991
Etiology (HBV/HCV/alcohol/other)	15/3/2/1 (71.4/14.3/9.5/4.8)	7/5/6/1 (36.8/26.3/31.6/5.3)	0.053
Child-Pugh score (5/6/7)	17/2/2 (81.0/9.5/9.5)	13/3/3 (68.4/15.8/15.8)	0.393
Tumor size (cm)	2.0 (1.0-3.0)	1.9 (1.0-3.0)	0.595
mUICC stage (I/II)	13/8 (61.9/38.1)	12/7 (63.2/36.8)	0.936
WBC (/mm ³)	4,520 (1,800-9,200)	5,310 (2,970-10,370)	0.542
Hemoglobin (g/dL)	13.4 (10.5-17.9)	11.9 (9.1-16.0)	0.172
Platelet counts ($\times 1,000/\text{mm}^3$)	138 (47-287)	89 (34-244)	0.063
Albumin (g/dL)	4.2 (3.3-4.9)	3.5 (3.1-4.9)	0.028
Bilirubin (mg/dL)	0.81 (0.41-1.49)	1.0 (0.23-4.0)	0.136
Prothrombin time (INR)	1.10 (0.90-1.23)	1.20 (0.95-1.80)	0.011
AFP (ng/mL)	8.23 (1.65-3,340)	14.01 (1.52-5,845)	0.278
PIVKA-II (mAU/mL)	33 (12-343)	68.5 (12-2,745)	0.075

Values are presented as number (%) or median (range).

DEB-TACE, drug-eluting bead transarterial chemoembolization; RFA, radiofrequency ablation; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; mUICC, modified International Union Against Cancer; WBC, white blood cell; INR, international normalized ratio; AFP, α -fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

*P-values were calculated using the Mann-Whitney U test, Student's t-test, Fisher exact test or chi-square test.

8. Statistical analysis

Results are summarized either as number (%), median (ranges) or mean (95% confidence interval [CI]) as appropriate. Continuous data were analyzed using the Mann-Whitney *U* test or student's *t*-test. Categorical data were evaluated using the Fisher exact test or chi-square test. Insufficient response to first treatment was censored at the time of first evaluation of therapeutic response. Follow-up loss or death without tumor recurrence was censored at the time of the last follow-up. Recurrence rates and curves were obtained using the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox regression was performed to

identify independent factors associated with tumor recurrence using variables with *P*-values less than 0.1 in univariate analysis. A *P*-value of less than 0.05 (2-tailed) was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium).

RESULTS

1. Clinical characteristics of the patients

The baseline characteristics of the patients are listed in Table 1. Twenty-one patients (52.5%) underwent DEB-TACE

Table 2. Tumor response after first treatment assessed by mRECIST

Tumor response	Complete response	Partial response	Stable disease	Progressive disease
DEB-TACE	19 (90.5)	1 (4.8)	1 (4.8)	0
RFA	18 (94.7)	0	0	1 (5.3)
<i>P</i> -value*	1.000	1.000	1.000	0.475

Values are presented as number (%).

mRECIST, modified Response Evaluation Criteria in Solid Tumors; DEB-TACE, drug-eluting bead transarterial chemoembolization; RFA, radiofrequency ablation.

**P*-values were calculated using Fisher exact test.

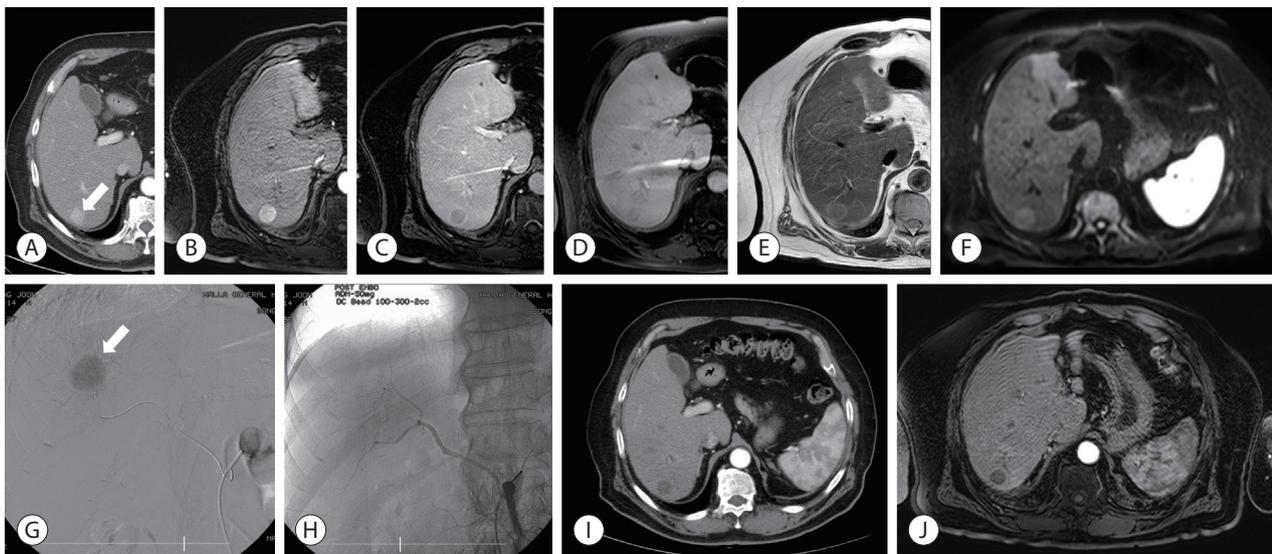


Figure 1. Solitary enhancing nodule measuring 2.0 cm in the liver segment 6 was noted on dynamic computed tomography (CT) (A: arterial phase, arrow) and gadoxetic acid-enhanced magnetic resonance imaging (MRI) (B: arterial, C: equilibrium, D: hepatobiliary phases, E: T2-weight, F: diffusion-weighted image) in 75-year-old male patient. Selective right hepatic arteriography demonstrated the faint tumor staining (G, arrow). Post-embolization arteriography (H) showed no more tumor staining and occlusion of the tumor supplying artery. Complete necrosis of the hepatocellular carcinoma nodule without remnant or new enhancement was observed on follow-up CT (I: arterial phase) and MRI (J: arterial phase). There is no local tumor recurrence 28.6 months after a single session of drug-eluting bead transarterial chemoembolization.

and 19 patients underwent RFA (11 ultrasound-guided and 8 CT-guided). The patients included 27 men and 13 women with median age of 67.5 years (range, 43-84). About 87% of the patients had Child-Pugh grade A liver function, and 60% of patients had ECOG performance grade of 0 while the remaining were either grade 1 or 2. The median tumor diameter was 2.0 cm (range, 1.0-3.0). There was no difference between the groups with regard to tumor stage ($P=0.936$). Although Child-Pugh scores of the two groups were not significantly different, the serum albumin of the RFA group was lower than that of the DEB-TACE group (4.2 vs. 3.5 g/dL, $P=0.028$) and prothrombin time international normalized

ratio of the RFA group was higher than that of DEB-TACE groups (1.10 vs. 1.20, $P=0.011$).

2. Tumor response

The target tumor responses evaluated after first treatment are summarized in Table 2. Complete response rates in DEB-TACE and RFA groups were 90.5% and 94.7%, respectively ($P=1.000$). In DEB-TACE group, partial response and stable disease rates were equally 4.8%. One patient (5.3%) in the RFA group showed progressive disease.

Fig. 1. describes the case of a patient with 2.0 cm-sized solitary enhancing nodule who experienced a complete ne-

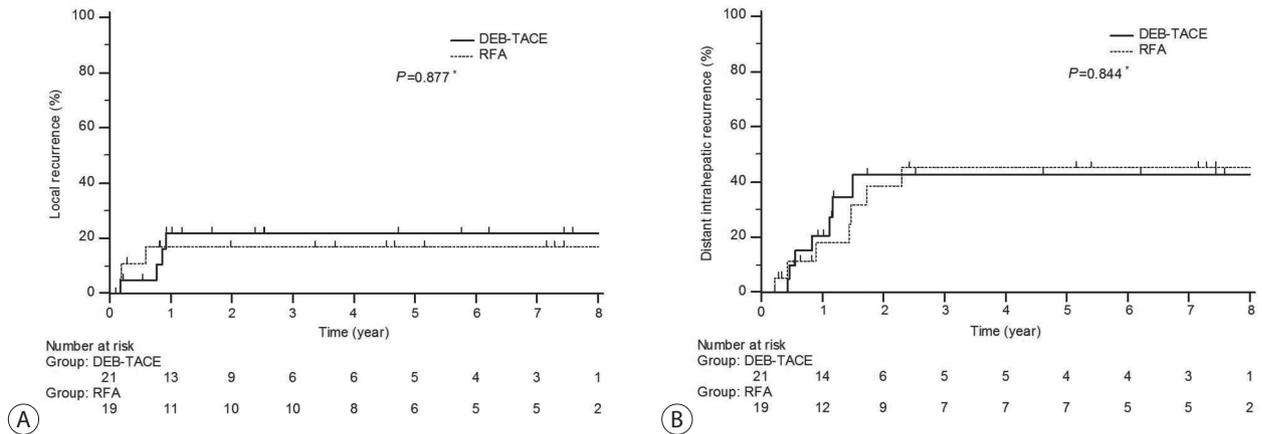


Figure 2. Estimated cumulative recurrence rate after drug-eluting bead transarterial chemoembolization (DEB-TACE) and radiofrequency ablation (RFA) for small hepatocellular carcinoma. Local (A) and distant intrahepatic (B) recurrences. * P -values were calculated using log-rank test for differences between two groups.

Table 3. Risk factors for local and distant intrahepatic recurrences

Variable	Univariate		Multivariate	
	HR (95% CI)	P -value*	HR (95% CI)	P -value*
Local recurrence				
PIVKA	1.001 (0.999-1.002)	0.086	-	-
Treatment modality	0.886 (0.199-3.975)	0.877	-	-
Distant intrahepatic recurrence				
Albumin	0.410 (0.169-0.993)	0.048	0.379 (0.153-0.937)	0.036
mUICC	2.920 (1.007-8.467)	0.049	0.499 (0.083-3.010)	0.449
Tumor size	3.651 (1.347-9.899)	0.011	8.197 (1.110-60.539)	0.039
Treatment modality	0.957 (0.333-2.752)	0.935	-	-

HR, hazard ratio; CI, confidence interval; PIVKA, protein induced by vitamin K absence or antagonist; mUICC, modified International Union Against Cancer.

* P -values were calculated using Cox regression hazard regression.

crisis on follow-up CT after a single session of DEB-TACE and underlines the absence of local tumor recurrence for 28.6 months.

3. Local and distant recurrences and risk factors related to recurrences

Overall mean follow-up duration for local recurrence was 87.6 months (95% CI, 74.4-102) and 65.6 months (95% CI, 48.6-82.6) for distant intrahepatic recurrence. Of the 21 patients who underwent DEB-TACE, one patient had partial response and one patient showed stable disease on first follow-up imaging. Local recurrences were noted in another four patients. Among 19 patients who received RFA, one patient showed progressive disease at first response evaluation and another three patients developed local recurrences. The 6- and 12-month cumulative local recurrence rate was 5.0%

and 21.8% in DEB-TACE vs. 11.1% and 17.0% in RFA group (Fig. 2A, $P=0.877$) and reached a plateau in 12 months. Distant intrahepatic recurrences developed in 14 cases during follow-up (7 and 7, respective groups). The 12- and 24-month cumulative distant intrahepatic recurrence rate was 20.6% and 42.7% in DEB-TACE vs. 17.2% and 36.3% in RFA group (Fig. 2B, $P=0.844$).

On Cox regression analysis with multivariable adjustment, there was no associated factor regarding local recurrence. Distant intrahepatic recurrence was significantly associated with albumin level and tumor size (Table 3). Treatment modality was not an independent risk factor for local or distant intrahepatic recurrences.

4. Safety

As treatment-related adverse events, there were no grade

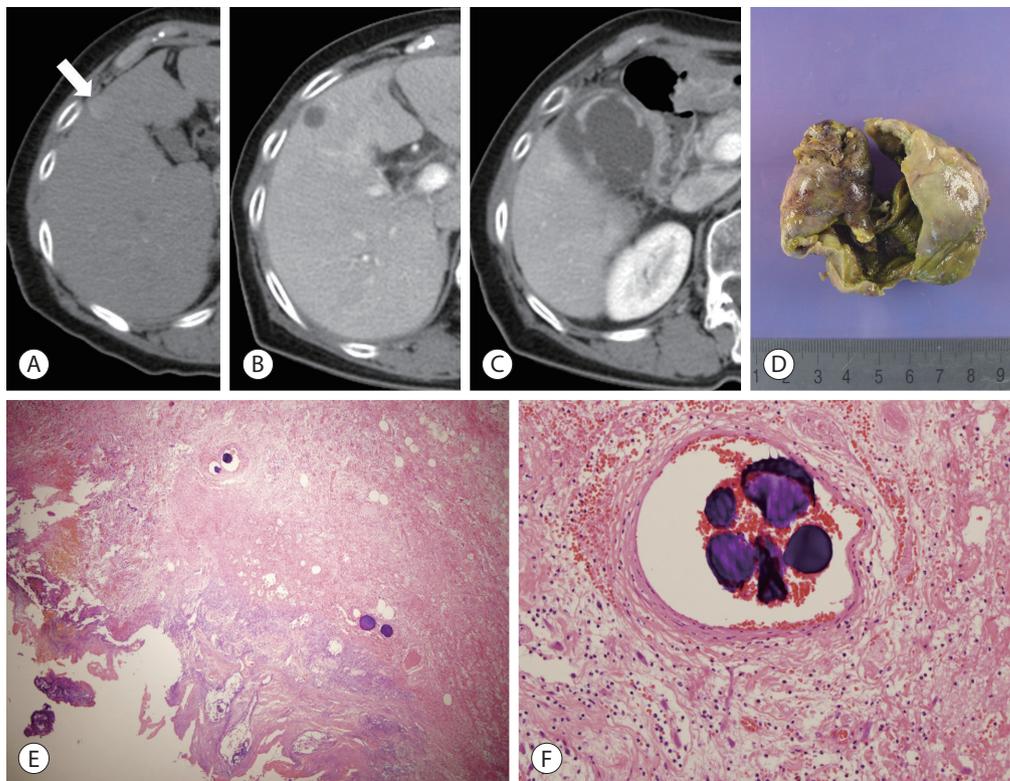


Figure 3. A 77-year-old woman who experienced acute cholecystitis requiring cholecystectomy after drug-eluting bead transarterial chemoembolization (DEB-TACE). 1.4 cm sized, typical hypervascular nodule with delayed washout at segment 5 (A, arrow) showed complete necrosis on dynamic computed tomography (CT) (B) that was taken 7 days after DEB-TACE. Acute cholecystitis impending gangrenous change was noted on the same follow-up CT (C). Emergency cholecystectomy was performed 10 days after DEB-TACE in spite of administration of antibiotics with vigorous intravenous hydration. Resected specimen revealed acute ischemic cholecystitis with deposition of embolic particles in the vessel (D, gross specimen; E, original magnification [x40]; F, original magnification [x200]).

3-4 laboratory toxicities in either group within 4 weeks and no mortality directly related to the procedures. Development of post-embolization or post-ablation syndrome under control with analgesic or antipyretic drugs was shown in 6 patients (28.6%) in DEB-TACE and 4 patients (21.1%) among RFA group. In RFA group, two patients experienced small pneumothorax (<2 cm rim present between the lung edge and chest wall) which was absorbed with supplemental oxygen within 1-2 days.

Two patients (9.5%) experienced gangrenous cholecystitis requiring cholecystectomy in DEB-TACE group. Fig. 3. illustrates one of these patients who underwent emergent operation and the biopsy resulted in ischemia due to deposition of embolic particles in the vessel. Another patient experienced liver abscess which required percutaneous catheter drainage.

DISCUSSION

In this study, we assessed retrospective data of 40 patients who underwent DEB-TACE or RFA for initial treatment of single small HCC. During a mean follow-up period of 87.6 months (95% CI, 74.4-102), 7 patients experienced local recurrence and 14 patients experienced distant intra-hepatic recurrence. The 6- and 12-month cumulative local recurrence rate was 5.0% and 21.8% in DEB-TACE vs. 11.1% and 17.0% in RFA group ($P=0.877$). The 12- and 24-month cumulative distant intrahepatic recurrence rate was 20.6% and 42.7% in DEB-TACE vs. 17.2% and 36.3% in RFA group ($P=0.844$).

In several practice guidelines, surgical resection and RFA are generally regarded as therapeutic strategies for patients of small HCC who have relatively good liver function and performance status.^{9,14-16} Previous articles regarding outcomes of RFA for treatment of small HCC (<5 cm) showed complete ablation in over 95% of cases.¹⁷ Two studies analyzed effectiveness of RFA for single small HCC up to 3 cm and local recurrences were reported 23.5-28.5% at 3 years and 27.9-32.1% at 5 years.^{18,19} However, there are several technical limitations and RFA-related complications although RFA appears to provide reasonable results comparable to surgical resection. Diminished effect or technical difficulty of RFA

could be encountered when the tumor is located adjacent to a major vessel (so-called "heat sink effect"), biliary tracts, critical extrahepatic organs (stomach, small and large intestines, gallbladder) or other structures (diaphragm, abdominal wall).¹⁷

From the anatomical aspect, the endoarterial approach could afford additionally safe therapeutic modality for aforementioned 'difficult-to-ablate' HCC cases. Compared with conventional TACE, DEB-TACE has been recognized to minimize drug-related side effects because it significantly improves drug delivery system by maximizing a constant concentration of the chemotherapeutic agents transported to the tumor while reducing the amount reaching the systemic circulation.^{20,21} In previous retrospective comparative study of conventional vs. DEB-TACE for small HCC, DEB-TACE provided more procedural safety than conventional TACE and tumor responses between two groups were not significantly different.²² However, as the authors revealed as a study limitation, the study focused on early-term data at 1 year.

Therefore, it is needed for subsequent studies on DEB-TACE compared to RFA, which is already known to be an acceptable curative treatment for small HCC. In this study, we analyzed relatively long-term follow-up data of patients who underwent DEB-TACE or RFA, and there were no significant differences in tumor response, local and distant intrahepatic recurrences between two groups. Two cases of cholecystitis as a complication of DEB-TACE developed early after initiation of DEB-TACE in our center and no additional non-target embolic side effects were reported subsequently.

The following limitations should be noted: 1) The study was a retrospective, single-center study and the number of enrolled patients was limited; and 2) the efficacy of DEB-TACE could be underestimated because treatment response was evaluated after one session of DEB-TACE or RFA. In a previous prospective DEB-TACE study, patients received up to three sessions of chemoembolization at 2-month intervals.²³ Further multicenter retrospective or prospective studies are needed to compare therapeutic efficacy between DEB-TACE and RFA or surgical resection.

In conclusion, tumor response and recurrence after DEB-TACE and RFA for treatment of small HCC is not significantly

different in this pilot study. Considering the procedure-related complications, DEB-TACE could be a bridging therapeutic option for local disease control in selective patients of small HCC if other therapeutic modalities are unfeasible.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethics Statement

This study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Cheju Halla General Hospital (IRB no. 2020-L09-01). The requirement for informed consent from patients was waived due to the retrospective nature of this study.

Funding Statement

No funding to declare.

Data Availability

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Study supervision: JDK.

All authors have reviewed and approved the final version of manuscript.

Supplementary Material

Supplementary data can be found with this article online <http://www.e-jlc.org/html/https://doi.org/10.17998/jlc.2021.05.20>.

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