# Effectiveness of drug-eluting bead transarterial chemoembolization versus conventional transarterial chemoembolization for small hepatocellular carcinoma in Child-Pugh class A patients

In Joon Lee* [ID], Jeong-Hoon Lee*, Yun Bin Lee, Yoon Jun Kim, Jung-Hwan Yoon, Yong Hu Yin, Myungsu Lee, Saebeom Hur, Hyo-Cheol Kim, Hwan Jun Jae and Jin Wook Chung [ID]

## Abstract

**Background:** This study aimed to compare the therapeutic effectiveness including progression-free survival (PFS), overall survival (OS), and safety of conventional transarterial chemoembolization (cTACE) and drug-eluting bead transarterial chemoembolization (DEB-TACE) in a superselective fashion for the patients with nodular hepatocellular carcinoma (HCC) ($n \leqslant 5$) and Child–Pugh class A.

**Methods:** A total of 198 consecutive patients with nodular HCCs ($n \leqslant 5$) and Child–Pugh class A liver function who were initially treated with cTACE ($n = 125$) or DEB-TACE ($n = 57$) were included retrospectively. The primary endpoint was PFS. Secondary endpoints included time-to-target lesion progression (TTTLP), OS, and safety.

**Results:** The median follow up was 62 months (range, 1–87 months). The PFS was significantly longer in the cTACE group than in the DEB-TACE group (median, 18 months *versus* 7 months; hazard ratio [HR] = 0.658, log-rank $p = 0.031$), whereas OS was comparable (log-rank $p = 0.299$). TTTLP was significantly longer in the cTACE group than in the DEB-TACE group (median, 34 months *versus* 11 months; log-rank $p < 0.001$). In the stratification analysis based on tumor size, the cTACE group showed significantly longer TTTLP than the DEB-TACE group in the 1.0–2.0 cm and 2.1–3.0 cm subgroups (HR = 0.188, log-rank $p < 0.001$ and HR = 0.410, $p = 0.015$, respectively) but not in the 3.1–5.0 cm and 5.1–10.0 cm subgroups (all $p > 0.05$). Postembolization syndrome occurred more frequently in the cTACE group than in the DEB-TACE group ($p = 0.006$).

**Conclusions:** DEB-TACE is followed by significantly shorter PFS than cTACE in patients with nodular HCCs ($n \leqslant 5$) and Child–Pugh class A, although OS is comparable. Postembolization syndrome occurs more frequently in cTACE than in DEB-TACE.

*Keywords:* drug-eluting bead, hepatocellular carcinoma, transarterial chemoembolization

Correspondence to:
**Jin Wook Chung**
Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
**chungjw@snu.ac.kr**

**In Joon Lee**
Department of Radiology, National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea

**Jeong-Hoon Lee
Yun Bin Lee
Yoon Jun Kim
Jung-Hwan Yoon**
Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea

**Yong Hu Yin
Myungsu Lee
Saebeom Hur
Hyo-Cheol Kim
Hwan Jun Jae**
Department of Radiology, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea

*Both author contributed equally to this work.

## Introduction

Since chemoembolization using iodized oil-based regimens was introduced in the 1980s, much evidence of its effectiveness and safety for the treatment of hepatocellular carcinoma (HCC) has been shown.[1] Currently, international guidelines recommend transarterial chemoembolization (TACE) for patients with HCC who are

unsuitable for potentially curative treatments;[2–4] in real-world practice, TACE is more widely used than guidelines recommend.[5] To improve local tumor control and clinical outcomes, TACE should be performed as selectively as possible through tumor-feeding arteries.[6–8] Owing to technical advances in flat panel detector and cone-beam computed tomography (CBCT), real-time fluoroscopy, digital subtraction angiography, and tomographic images can be acquired in a single angiography unit.[9] CBCT provides additional information on the tumor and its feeding arteries, which can be helpful in treatment planning and navigation for superselective TACE.[10,11]

Because conventional TACE (cTACE) uses iodized oil emulsion mixed with anticancer drug, its pharmacokinetics have disadvantages.[12,13] Some portion of chemotherapeutic agents can be released into the systemic circulation, so may cause systemic side effects.[14] To overcome this, drug-eluting bead (DEB) TACE has been used to enhance sustained and tumor-selective drug delivery.[12,15] In the PRECISION V study, the first such randomized trial at European centers, DEB-TACE failed to achieve superior overall survival (OS) compared with cTACE.[16] However, DEB-TACE provides a better safety profile than cTACE, but only for patients with more advanced liver disease.[17] Among the whole study population, DEB-TACE only differed significantly from cTACE in less hair loss in the DEB-TACE group, most likely due to lower peak concentrations of doxorubicin. Subsequent studies were conducted, but a superiority of DEB-TACE over cTACE has not yet been clearly established.[18,19] Conflicting results of several meta-analyses suggest that controversy about this issue remains.[20–22] Recently, the European Association for the Study of the Liver stated that, presently, evidence is insufficient to recommend one TACE technique over another.[4] Moreover, selective TACE with CBCT was not performed in most previous studies. Thus, reevaluation of the effectiveness of cTACE *versus* DEB-TACE is warranted in the era of superselective TACE with CBCT to determine which group of patients will benefit most from either cTACE or DEB-TACE.

The purpose of this study was to compare how TACE and DEB-TACE, both performed superselectively using CBCT, affect progression-free survival (PFS), OS, and safety for patients with nodular HCC ($n \leqslant 5$) and Child–Pugh class A liver function.

## Materials and methods

### Patients
This study included consecutive patients who underwent CBCT-guided superselective cTACE or DEB-TACE as their initial treatment for nodular HCCs (tumor number $\leqslant 5$) without vascular invasion or metastasis, between January 2011 and April 2013 at a single tertiary medical center (Seoul National University Hospital, Seoul, Korea). The diagnosis of HCC was based either on histological findings or on the American Association for the Study of Liver Diseases (AASLD) noninvasive criteria.[2] During the study period, DEB-TACE was more expensive than cTACE in our country because national health insurance covered cTACE but not DEB-TACE. Therefore, based on the results of previous studies, we explained the potential advantages (i.e. less postembolization syndrome) and disadvantages (i.e. high cost in spite of similar effectiveness) of DEB-TACE compared with cTACE to the patients before treatment and let them choose between these two options.

Exclusion criteria were (i) HCC initially presented as a ruptured HCC, (ii) hepatic dysfunction classified as a Child–Pugh class B or C, (iii) age <20 or >80 years, (iv) current or previous malignancies other than HCC, and (v) other severe comorbidities such as end-stage renal disease or biliary tract disease. Patients who underwent another anticancer treatment in combination with cTACE or DEB-TACE within a week without follow-up imaging study were regarded as combination therapy, considered as a different treatment modality.

During the study period, among 859 patients who were initially treated with chemoembolization, 335 patients met the inclusion criteria. According to the exclusion criteria, 124 patients were excluded. After reviewing radiological images, 13 patients did not have typical enhancing nodules that met imaging diagnosis criteria of HCC.[2] Finally, 182 patients were included in this study: 125 patients in the cTACE group and 57 patients in the DEB-TACE group (Figure 1). Baseline characteristics of the study population were investigated. HCC stages were evaluated according to the modified Union for International Cancer Control (mUICC) and the Barcelona Clinic Liver Cancer (BCLC) staging systems.[2,23] Portal hypertension was defined as varices on endoscopy or CT image, ascites requiring diuretic treatment, or
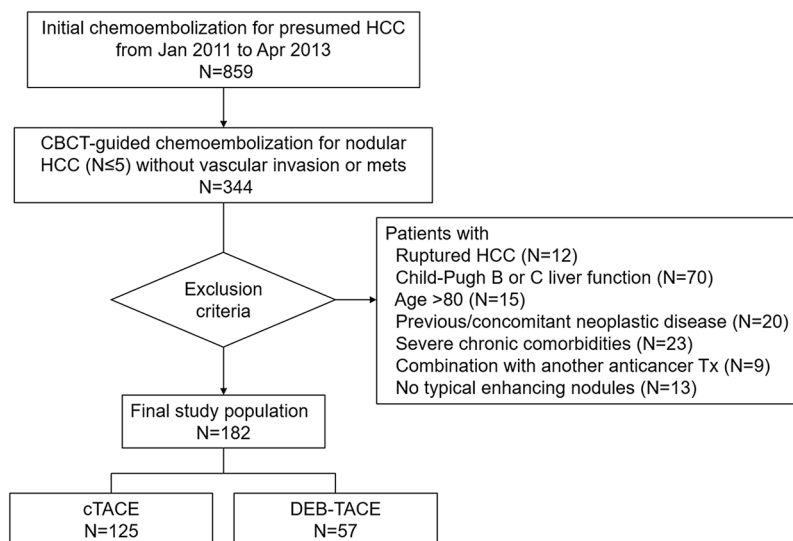
**Figure 1.** Flowchart of patient selection.

splenomegaly (⩾12 cm) with thrombocytopenia (<100,000/mm³).[24]

The study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (No. 1606-132-772). The requirement for written informed consent from patients was waived by the Institutional Review Board because clinical data were analyzed anonymously in this study.

### TACE procedure and follow up

CBCT-guided superselective TACE was performed by two radiologists (J.W.C. and H.C.K.) with >10 years of experience in interventional oncology. Based on CBCT images, obtained using the protocol described previously (see the Supplemental Material),[25] TACE was performed as selectively as possible through tumor-feeding arteries by using a microcatheter with a 2.0-F tip (Progreat Alpha; Terumo, Tokyo, Japan).

In cTACE, an emulsion of 2–10 ml of iodized oil (Lipiodol; Guerbet, Roissy, France) and 10–50 mg doxorubicin hydrochloride powder (Adriamycin RDF; Ildong Pharmaceutical Co., Seoul, Korea), depending on the tumor burden, dissolved in iodinated contrast agents in a 4:1 (iodized oils:doxorubicin solution) volume ratio, was slowly infused until it covered all tumors or an oily portogram appeared around the tumors.

Additional embolization was performed with gelatin sponge particles until near-stasis of arterial flow.

In DEB-TACE, one vial of DEB agent (DC Bead; Biocompatibles UK, Farnham, UK) was loaded with 50–70 mg of doxorubicin for 2 hours, and the preparation was suspended in 50 ml of a mixture of normal saline and iodinated contrast agent prepared at a 1:1 ratio. One or two vials of DEB agent were used, 100–300 μm DEB agent was used in every patient; an additional 300–500 μm DEB agent was used in five patients with large tumors. DEB agent was slowly infused through tumor-feeding arteries until near-stasis of arterial flow. If blood pools remained with a disappearance of tumor stain, gelatin sponge particles were used.

An initial follow-up dynamic CT or MRI with gadoxetic acid disodium (Primovist; Schering Pharma, Berlin, Germany) enhancement was performed 1–3 months after the treatment, and follow-up imaging interval was 2–4 months. Complete blood count, liver biochemical tests, tumor markers such as alfa-fetoprotein (AFP) or PIVKA-II, and serum creatinine were also measured. The imaging interval was based on the clinical situation such as tumor staining during TACE, changes in serum tumor markers, and patient's general condition. In patients with complete response (CR), the follow-up interval was increased to up to 4 months. Further treatments were dependent on clinical evaluation, laboratory

findings, and imaging response. Additional treatment that was received after tumor recurrence were reviewed and recorded.

### Endpoints and assessments

The tumors were allocated to the target lesion and the nontarget lesion, and tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) using radiological imaging by three interventional radiologists (see the Supplemental Material).[26]

Index dates were set as the date of the first transarterial treatment (either cTACE or DEB-TACE). The primary endpoint was PFS. PFS was measured from the index date to the first tumor progression, to death from any cause, or censored date. Secondary endpoints included time-to-target lesion progression (TTTLP) in per-lesion analysis, OS, and safety in per-patient analysis. TTTLP was measured from the index date to the first local tumor progression of the target lesion. OS was measured from the index date to any cause of death. In the assessment of PFS and OS, survival time was censored at the date of performing liver transplantation or at the date of last follow up in patients whose survival status could not be confirmed in the database of the national health care system. Time-to-local progression (TTLP) and time-to-progression were also analyzed (see the supplemental material).

To evaluate local tumor control of each tumor, related to the tumor size, per-lesion analysis was also performed for relevant lesions treated by TACE. Tumor response was categorized as CR, partial response (PR), stable disease (SD), and progressive disease (PD) based on the diameter change of the viable portions, and TTTLP was calculated. For subgroup analysis based on the tumor size, target lesions were categorized into 1.0–2.0, 2.1–3.0, 3.1–5.0, and 5.1–10.0 cm according to maximal tumor diameter.

Adverse event and laboratory test assessments were based on the Common Terminology Criteria for Adverse Events, version 5.0.[27] All adverse events considered to be related to the procedure were analyzed, and postembolization syndrome was clinically diagnosed during the postprocedural hospital stay.[28] Serious adverse events were defined as any event resulting in death, any life-threatening consequences, persistent or significant disability or incapacity, unscheduled hospital visit, or prolongation of hospitalization. Prolongation of hospitalization was defined as lasting more than 7 days. Results of laboratory tests performed 1 month after the treatment were compared between the two groups. To assess liver and biliary injuries, medical records and follow-up imaging studies were reviewed for bile duct dilatation, significant bile duct injury, liver abscess, and biloma. Significant bile duct injury was defined as prominent bile duct dilatation that was wider than segmental distribution.

### Statistical analysis

Categorical variables were reported as counts and percentages, and continuous variables were reported as means and standard deviations. The patients were characterized by demographic and clinical variables, and comparisons between the two groups were performed by using the Fisher's exact test, chi-squared test, or Student's *t* test. Initial, 6-month, 1-year, 2-year, 3-year, 4-year, and 5-year overall tumor responses were assessed. Survival and recurrence were plotted using the Kaplan–Meier method and compared using the log-rank test. Treatment effects between the two groups were compared using univariable analysis and multivariable Cox proportional hazard models. The latter was adjusted for potential prognostic factors defined as variables with $p < 0.2$ in univariable analysis. A two-tailed $p$ value of $<0.05$ was considered statistically significant. All statistical analyses were performed by using SPSS version 18.0 (SPSS, Inc., IBM, Chicago, IL).

## Results

### Baseline characteristics

The baseline characteristics of the study population and the target lesions are summarized in Tables 1 and 2. The most common etiology of underlying liver disease was chronic hepatitis B, and >80% of patients had stage II or III HCCs according to the mUICC. Among the whole study population, 134 of 182 (73.6%) had at least one tumor smaller than 3 cm. Baseline patient and tumor characteristics did not differ significantly between the cTACE and DEB-TACE groups although the DEB-TACE group tended to have slightly larger tumors.

### Tumor response

The tumor response is summarized in Table 3. In the follow-up period, CR occurred more frequently

**Table 1.** Baseline characteristics of the study population.

| Patients | | | |
|---|---|---|---|
| **Parameters** | **cTACE (*n* = 125)** | **DEB-TACE (*n* = 57)** | ***p* value** |
| Age | 60.94 ± 9.45 | 62.63 ± 9.16 | 0.262 |
| Gender (male/female) | 104 (83.2)/21 (16.8) | 48 (84.2)/9 (15.8) | 1.000 |
| Hepatitis B surface antigen | 97 (77.6) | 42 (73.7) | 0.577 |
| Anti-hepatitis C virus | 15 (12.0) | 10 (17.5) | 0.355 |
| Platelet ($10^3$/mm$^3$) | 127.05 ± 52.03 | 136.72 ± 64.84 | 0.284 |
| Serum albumin (g/dL) | 3.85 ± 0.41 | 3.87 ± 0.39 | 0.692 |
| Total bilirubin (mg/dL) | 0.87 ± 0.40 | 0.85 ± 0.36 | 0.746 |
| PT (INR) | 1.05 ± 0.08 | 1.05 ± 0.08 | 0.939 |
| Creatinine (mg/dL) | 0.85 ± 0.18 | 0.89 ± 0.17 | 0.224 |
| Ascites (absent/present) | 122 (97.6)/3 (2.4) | 55 (96.5)/2 (3.5) | 0.649 |
| Portal hypertension (absent/present) | 52 (41.6)/73 (58.4) | 24 (42.1)/33 (57.9) | 1.000 |
| Child–Pugh class (A5/A6) | 88 (70.4)/37 (29.6) | 41 (71.9)/16 (28.1) | 0.862 |
| ECOG (0/1) | 115 (92.0)/10 (8.0) | 51 (89.5)/6 (10.5) | 0.581 |
| AFP (≤200ng/mL/>200ng/mL) | 110 (88.0)/15 (12.0) | 50 (87.7)/7 (12.3) | 1.000 |
| Maximum tumor size (cm) | 3.08 ± 1.62 | 3.47 ± 1.74 | 0.143 |
| Maximum tumor size | | | 0.482 |
|     1.0–2.0 cm | 33 (26.4) | 10 (17.5) | |
|     2.1–3.0 cm | 41 (32.8) | 19 (33.3) | |
|     3.1–5.0 cm | 35 (28.0) | 17 (29.8) | |
|     5.1–10.0 cm | 16 (12.8) | 11 (19.3) | |
| Patients with at least one tumor <3 cm | 91 (72.8) | 43 (75.4) | 0.856 |
| Number of tumors | 1.76 ± 0.97 | 2.02 ± 1.17 | 0.122 |
| Tumor multiplicity (single/multiple) | 65 (52.0)/60 (48.0) | 24 (42.1)/33 (57.9) | 0.263 |
| mUICC | | | 0.205 |
|     I | 18 (14.4) | 4 (7.0) | |
|     II | 62 (49.6) | 26 (45.6) | |
|     III | 45 (36.0) | 27 (47.4) | |
| BCLC | | | 0.313 |
|     Stage 0 | 16 (12.8) | 4 (7.0) | |
|     Stage A | 82 (65.6) | 36 (63.2) | |
|     Stage B | 27 (21.6) | 17 (29.8) | |
| Milan criteria (within/beyond) | 88 (70.4)/37 (29.6) | 35 (61.4)/22 (38.6) | 0.237 |

**Table 2.** Baseline characteristics of the target lesions.

| Target lesions | | | |
|---|---|---|---|
| **Parameters** | **cTACE (*n* = 165)** | **DEB-TACE (*n* = 83)** | ***p*-value** |
| Tumor size (cm) | 2.73 ± 1.56 | 2.94 ± 1.68 | 0.335 |
| Tumor size | | | 0.811 |
|    1.0–2.0 cm | 65 (39.4) | 29 (34.9) | |
|    2.1–3.0 cm | 48 (29.1) | 24 (28.9) | |
|    3.1–5.0 cm | 36 (21.8) | 19 (22.9) | |
|    5.1–10.0 cm | 16 (9.7) | 11 (13.3) | |

AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; mUICC, modified Union for International Cancer Control; PT, prothrombin time.
*Note*: Data are expressed as *n* (%) or mean ± standard deviation. The BCLC staging system modified by AASLD guidance 2018 are used.

**Table 3.** Tumor response analysis of the patients.

| | cTACE | | | | | | DEB-TACE | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **No. at risk** | **CR** | **OR (CR+PR)** | **PD** | **Censored cases** | | **No. at risk** | **CR** | **OR (CR+PR)** | **PD** | **Censored cases** | |
| | | | | | **Treatment Conversion** | **F/U loss** | | | | | **Treatment Conversion** | **F/U loss** |
| Best | 125 | 98 (78.4) | 117 (93.6) | 7 (5.6) | – | – | 57 | 29 (50.9) | 54 (94.7) | 1 (1.8) | – | – |
| 6 months | 115 | 77 (67.0) | 90 (78.3) | 25 (21.7) | 8 | 2 | 45 | 17 (37.8) | 21 (46.7) | 24 (53.3) | 12 | 0 |
| 12 months | 110 | 62 (56.4) | 66 (60.0) | 44 (40.0) | 13 | 2 | 43 | 10 (23.3) | 11 (25.6) | 32 (74.4) | 14 | 0 |
| 24 months | 108 | 39 (36.1) | 41 (38.0) | 67 (62.0) | 13 | 4 | 42 | 8 (19.0) | 8 (19.0) | 34 (81.0) | 14 | 1 |
| 36 months | 107 | 28 (26.2) | 28 (26.2) | 79 (73.8) | 13 | 5 | 42 | 8 (19.0) | 8 (19.0) | 34 (81.0) | 14 | 1 |
| 48 months | 106 | 22 (20.8) | 22 (20.8) | 84 (79.2) | 14 | 5 | 42 | 6 (14.3) | 6 (14.3) | 36 (85.7) | 14 | 1 |
| 60 months | 99 | 19 (19.2) | 13 (13.1) | 86 (86.9) | 14 | 6 | 40 | 5 (12.5) | 4 (10.0) | 36 (90.0) | 14 | 2 |
| Causes of PD | LTP: 28 (32.6) IDR: 51 (59.3) | LTP & IDR: 7 (8.1) | | | | | LTP: 20 (55.5) IDR: 9 (25.0) | LTP & IDR: 7 (19.4) | | | | |

CR, complete response; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; IDR, intrahepatic distant recurrence; F/U, follow up; LTP, local tumor progression; OR, objective response; PD, progressive disease.
*Note*: Data are expressed as *n* (%).
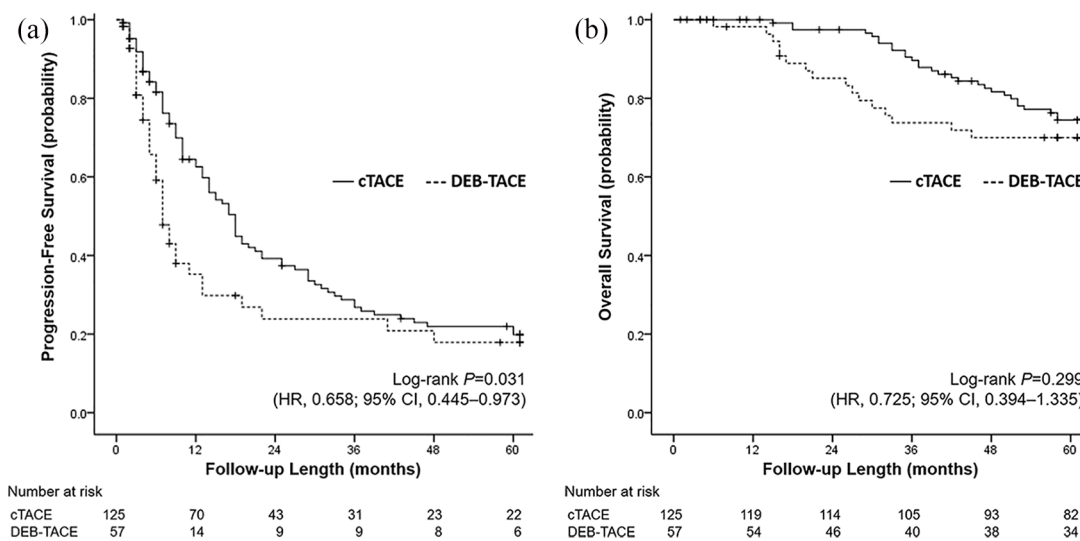
**Figure 2.** Kaplan–Meier estimates of (a) progression-free survival and (b) overall survival.

in the cTACE group than in the DEB-TACE group (78.4% *versus* 50.9%; $p < 0.001$) although objective response rates were comparable (93.6% *versus* 94.7%; $p = 0.765$).

## PFS

Median follow-up duration was 62 months (range, 1–87 months) in the whole study population: 62 months (range, 2–82 months) in the cTACE group and 58 months (range, 1–87 months) in the DEB-TACE group. During follow up, 88 patients (70.4%) in the cTACE group and 36 (63.2%) in the DEB-TACE group experienced disease progression or died. The PFS was significantly longer in the cTACE group than in the DEB-TACE group (hazard ratio [HR], 0.658; 95% confidence interval [CI], 0.445–0.973; log-rank $p = 0.031$). Median PFS was 18 months in the cTACE group and 7 months in the DEB-TACE group (Figure 2). In multivariable analysis, cTACE was associated with significantly lower risk of tumor progression or death (adjusted HR [aHR], 0.624; 95% CI, 0.418–0.931; $p = 0.021$) after adjusting for tumor number (single *versus* multiple) (Table 4). In addition, in a subgroup of BCLC stage B HCC, which is an original indication for TACE according to BCLC treatment algorithm, PFS was significantly longer in the cTACE group than in the DEB-TACE group (HR = 0.290, 95% CI = 0.133–0.628, log-rank $p = 0.001$) (Supplementary Figure 1).

## TTTLP and subgroup analysis of the target lesions

TTTLP was significantly longer in the cTACE group than in the DEB-TACE groups (log-rank $p = 0.029$) (Figure 3(a)). Median TTTLP was 12 months in the DEB-TACE group, but was not reached in the cTACE group. In the stratified subgroup analysis based on tumor size, the cTACE group had significantly longer TTTLP than the DEB-TACE group among the 1.0–2.0 cm (HR, 0.188; 95% CI, 0.096–0.367; log-rank $p < 0.001$) and 2.1–3.0 cm subgroups (HR, 0.410; 95% CI, 0.193–0.870; log-rank $p = 0.015$), but not among the 3.1–5.0 cm and 5.1–10.0 cm subgroups (Figure 3). In the cTACE group, as expected, target lesion progression became longer with increasing tumor size. Surprisingly, however, the DEB-TACE group had significantly shorter TTTLP in the 1.0–2.0 cm tumors than in the 2.1–5.0 cm tumors (log-rank $p = 0.036$) (Figure 3(f)).

## OS

During follow up, 37 patients (29.6%) in the cTACE group and 17 (29.8%) in the DEB-TACE group died. OS was not significantly different between the cTACE and DEB-TACE groups (HR 0.725, 95% CI 0.394–1.335, log-rank $p = 0.299$) (Figure 2(b)). The cumulative survival rates at years 1, 2, 3, and 5 were 100%, 97.4%, 89.6%, and 74.5% in the cTACE group and 98.2%, 85.1%, 73.8%, and 70.0% in the DEB-TACE group, respectively.

**Table 4.** Univariable and multivariable analysis of prognostic factors for progression-free survival.

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *p* value | Hazard ratio | 95% CI | *p* value |
| Group (cTACE *versus* DEB-TACE) | 0.658 | 0.445, 0.973 | 0.036 | 0.624 | 0.418, 0.931 | 0.021 |
| Age (>65 *versus* ≤65) | 1.055 | 0.731, 1.055 | 0.777 | | | |
| Gender (male *versus* female) | 0.871 | 0.557, 1.362 | 0.544 | | | |
| HBsAg (positive *versus* negative) | 1.024 | 0.682, 1.538 | 0.909 | | | |
| Anti-HCV (positive *versus* negative) | 1.589 | 0.990, 2.550 | 0.055 | 1.212 | 0.732, 2.007 | 0.455 |
| Platelet (≤120,000/mm³ *versus* >120,000/mm³) | 1.175 | 0.826, 1.674 | 0.370 | | | |
| Serum albumin (≤3.5 g/dL *versus* >3.5 g/dL) | 1.467 | 0.997, 2.167 | 0.052 | 1.455 | 0.966, 2.194 | 0.073 |
| Total bilirubin (>1.0 mg/dL ≤1.0 mg/dL) | 1.393 | 0.936, 2.073 | 0.099 | 1.301 | 0.864, 1.959 | 0.207 |
| PT INR (>1.2 *versus* ≤1.2) | 0.830 | 0.339, 2.033 | 0.684 | | | |
| Creatinine (>1.0 mg/dL *versus* ≤1.0 mg/dL) | 0.924 | 0.637, 1.340 | 0.676 | | | |
| Ascites (present *versus* absent) | 0.871 | 0.321, 2.362 | 0.786 | | | |
| Portal hypertension (present *versus* absent) | 1.142 | 0.796, 1.638 | 0.470 | | | |
| ECOG (1 *versus* 0) | 1.455 | 0.781, 2.710 | 0.238 | | | |
| AFP (>200 ng/mL *versus* ≤200 ng/mL) | 1.256 | 0.762, 2.072 | 0.372 | | | |
| Maximum tumor size (>3 cm *versus* ≤3.0 cm) | 1.478 | 0.958, 2.281 | 0.077 | 1.390 | 0.896, 2.157 | 0.142 |
| Tumor multiplicity (multiple *versus* single) | 1.729 | 1.208, 2.476 | 0.003 | 1.683 | 1.162, 2.439 | 0.006 |

AFP, alpha-fetoprotein; CI, confidence interval; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead chemoembolization; ECOG, Eastern Cooperative Oncology Group; HCV, hepatitis C virus; HR, hazard ratio; INR, international normalized ratio; PT, prothrombin time.

### Safety

Incidence of adverse events is summarized in Table 5. Postembolization syndrome occurred more frequently in the cTACE group than in the DEB-TACE group ($p = 0.006$). The most common symptoms in the cTACE group were abdominal pain, followed by nausea, fever, and vomiting. The patients in the cTACE group remained hospitalized for 0.8 days longer (mean) than the DEB-TACE group ($p = 0.001$). All patients in the DEB-TACE group were discharged the day after the treatment, but 62 (49.6%) patients in the cTACE group stayed a few more days. Five (4.0%) patients in the cTACE group experienced prolonged hospitalization, longer than 7 days. Unscheduled hospital visits were also more frequent in the cTACE group ($p = 0.024$).

At 1 month after the treatment, Child–Pugh score and laboratory toxicity categories did not differ significantly between the two groups. Although bile duct dilatation occurred more frequently in the DEB-TACE group, the development of significant bile duct injury, biloma, or liver abscess did not differ significantly between the two groups.

### Discussion

In this study, cTACE was followed by significantly longer PFS than DEB-TACE after treatment for nodular HCCs ($n \leq 5$). The cTACE was followed by significantly longer time until both local tumor progression and overall progression than was DEB-TACE, although OS did not differ by type of TACE. The longer PFS of cTACE was
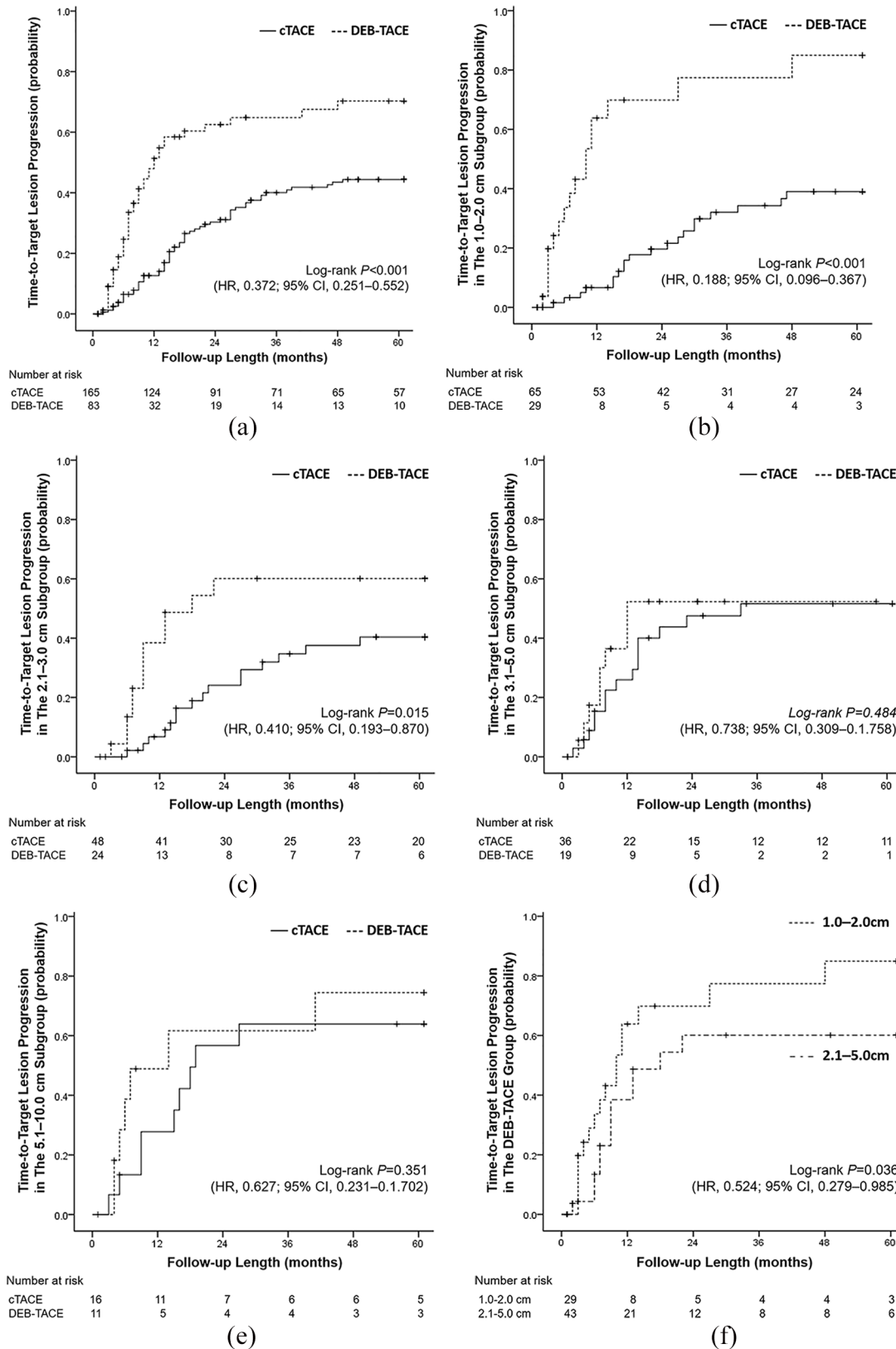
**Figure 3.** Kaplan–Meier estimates of time-to-target lesion progression (a) in all target lesions, (b) in the 1.0–2.0 cm tumors, (c) in the 2.1–3.0 cm tumors, (d) in the 3.1–5.0 cm tumors, (e) in the 5.1–10.0 cm tumors, and (f) in the DEB-TACE group.

**Table 5.** Adverse events and toxicities according to the treatment group.

| Parameter | cTACE (*n* = 125) | DEB-TACE (*n* = 57) | *p* value |
|---|---|---|---|
| Postembolization syndrome | 80 (64.0) | 24 (42.1) | 0.006 |
|    Fever | 27 (21.6) | 3 (5.3) | 0.005 |
|    Nausea | 46 (36.8) | 9 (15.8) | 0.005 |
|    Vomiting | 25 (20.0) | 4 (7.0) | 0.029 |
|    Anorexia | 4 (3.2) | 0 (0.0) | 0.311 |
|    Abdominal Pain | 80 (64.0) | 22 (38.6) | 0.002 |
|    Hypertension/hypotension/bradycardia | 20 (16.0) | 2 (3.5) | 0.015 |
| Hospitalization duration (days) | 2.3 ± 1.98 | 1.5 ± 0.65 | 0.001 |
| Prolonged hospitalization (>7 days) | 5 (4.0) | 0 (0.0) | 0.327 |
| Unscheduled hospital visit | 19 (15.2) | 2 (3.5) | 0.024 |
|    ER visit/Readmission | 15 / 4 (12.0 / 3.2) | 1 / 1 (1.8 / 1.8) | |
| Increased Child–Pugh score after 1 month | 10 (8.0) | 7 (12.3) | 0.413 |
| Laboratory toxicity after 1 month | | | |
|    PT-INR (grade 0/1/2) | 82 / 16 / 0 (83.7 / 16.3 / 0.0) | 47 / 6 / 0 (88.7 / 11.3 / 0.0) | 0.476 |
|    Albumin (grade 0/1/2) | 116 / 8 / 0 (93.5 / 6.5 / 0.0) | 53 / 3 / 1 (93.0 / 5.3 / 1.8) | 0.322 |
|    Total bilirubin (grade 0/1/2) | 105 / 15 / 4 (84.7 / 12.1 / 3.2) | 50 / 4 / 3 (87.7 / 7.0 / 5.3) | 0.491 |
|    AST (grade 0/1/2/3) | 81 / 41 / 1 / 1 (65.3 / 33.1 / 0.8 / 0.8) | 38 / 19 / 0 / 1 (64.9 / 33.3 / 0.0 / 1.8) | 0.854 |
|    ALT (grade 0/1/2/3) | 77 / 42 / 3 / 2 (62.1 / 33.9 / 2.4 / 1.6) | 39 / 15 / 1 / 2 (68.4 / 26.3 / 1.8 / 3.5) | 0.645 |
| Bile duct dilatation | 15 (12.0) | 25 (43.9) | <0.001 |
| Significant bile duct injury | 9 (7.2) | 4 (7.0) | 1.000 |
| Biloma formation | 5 (4.0) | 0 (0.0) | 0.327 |
| Liver abscess formation | 2 (1.6) | 0 (0.0) | 1.000 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ER, emergency room; INR, international normalized ratio; PT, prothrombin time.
*Note*: Data are expressed as *n* (%) or mean ± standard deviation.

attributed to the fact that cTACE was followed by significantly better tumor control for HCC with maximal tumor size less than 3.0 cm than was DEB-TACE.

The better local tumor response of cTACE for small HCC can be explained by the physical properties of the lipiodol-based emulsion. It can pass through fine tumor-feeding arteries, reach tumor vessels, penetrate deeply into the tumor capsule, and accumulate in the peritumoral portal vein through presinusoidal arterioportal communication or tumor drainage route.[29–31] With cTACE, local tumor recurrence was reportedly

lower when more portal veins were visualized during the procedure.[32] The diameter of a tumor-feeding artery is significantly correlated with tumor size.[33] Feeding arteries of small tumors are not hypertrophied yet, and dominant arterial flow to the tumor is not yet sufficiently developed. Moreover, portal venous supply remains in the early stage of hepatocarcinogenesis.[34] In cTACE, because CBCT can identify small tumors and fine tumor-feeding arteries better than conventional angiography, intratumoral vessels and peritumoral portal veins can be filled with a sufficient amount of lipiodol emulsion by using a superselective approach, which can induce complete tumor necrosis.[35] This study demonstrated that the therapeutic effect of cTACE was better in smaller HCCs, which met the usual expectation for locoregional treatment.

In contrast, this study demonstrated that DEB-TACE was followed by significantly worse tumor response for smaller HCCs (1.0–2.0 cm) than for larger HCCs (2.1–5.0 cm), which was not expected. The impaired tumor response of DEB-TACE for small HCCs might be explained by the inherent disadvantage of particulate embolic material, which cannot pass through vessels smaller than the DEBs used and cannot manage portal venous supply to the tumor. In a catheter-assisted CT angiography study, smaller tumors had smaller feeding arteries and the main tumor-feeding artery was frequently smaller than 0.2 mm in diameter when the tumor was smaller than 3 cm in size.[33] In small HCCs, 100–300 μm DEBs may not penetrate into intratumoral vessels in sufficient quantities despite performing selective TACE. A previous study reported that the median diameter of vessels occluded by DEB was 208 μm, and just 42% of the occluded vessels were located inside the tumor when DEB-TACE was performed for 3.9 cm tumors with 100–300 μm DEBs.[36] Recently, chemoembolization with small calibrated microspheres less than 100 μm was introduced.[37,38] Smaller DEB may increase local tumor response by overcoming disadvantage of larger DEB, but it may also increase the risk of ischemic injury owing to closely related adverse events, such as postembolization syndrome and biliary complication. A well-designed prospective study is warranted to determine whether smaller DEB can improve therapeutic outcomes for small HCCs.

As reported by previous studies, our study also found that long-term OS did not differ significantly between the two groups, however, cTACE was superior to DEB-TACE in local tumor response especially for small tumors. The present study involved only patients with good liver function without any other severe chronic comorbidity. Furthermore, additional active treatment was administered after tumor recurrence using multidisciplinary approaches. As a result, 5-year OS exceeded 70% in both groups, which was much higher than is usually expected.[34] Thus, the number of deaths may have limited statistical power to detect a statistical difference. However, it is noteworthy that the risk of death was 27.5% lower in the cTACE group; hence, further long-term follow up is warranted.

Postembolization syndrome occurred more frequently in the cTACE group than in the DEB-TACE group; this, probably explains their longer hospital stays and more frequent unscheduled hospital visits. A possible mechanism for this difference follows. The liver capsule is covered with fine capsular arterial plexus that is a potential collateral pathway between the isolated hepatic artery and extrahepatic collateral artery.[39] This hepatic capsular plexus can be filled with lipiodol-based emulsion because it can penetrate more deeply than DEBs, which can cause severe ischemic pain and hepatic capsular irritation. Notably, nerve fibers that sense pain are present in the liver capsule, but not in the liver parenchyma.

According to previous studies, DEB-TACE provides a better safety profile than cTACE in advanced patients,[17] but this difference was more frequently related to biliary injury.[40] However, in the present study, at 1 month after chemoembolization, hepatotoxicity did not differ significantly between the two groups. Although minimal bile duct dilatation occurred more frequently in the DEB-TACE group, clinically significant biliary injury, biloma formation, and liver infarction were not more frequent in the DEB-TACE group. This was probably because the treated area was well restricted by the superselective approach used in this study. Performing chemoembolization using a superselective approach may have a greater effect on decreasing hepatic and biliary complications than the choice of cTACE or DEB-TACE.

In summary, cTACE and DEB-TACE can be used appropriately, that is selectively and strategically, depending on clinical situation to maximize the advantage of each strategy. For an example,

staged treatment using DEB-TACE followed by cTACE can be useful strategy for elderly patients with multiple HCCs (maximum diameter >5 cm): DEB-TACE could be initially performed to control large main tumors, which could shorten the time to next treatment due to less-severe postembolization syndrome. Then, as a second treatment, cTACE can be performed for residual lesions including multiple small tumors to enhance effectiveness of treatment.

This study had a few limitations. First, considerable selection bias was inevitable in this study because of its retrospective nature, its nonrandomized design, and inclusion of only patients with Child–Pugh class A liver function. Performing propensity score matching owing to the small number of patients was impossible due to the many variables and the significant data loss that matching would entrail. However, some bias should have been resolved by the multivariable Cox regression analysis. Further well-designed prospective studies are warranted to confirm the results of this study. Second, among the whole study population, 122 of 182 (67.0%) underwent additional treatment for recurrent HCC after the first TACE. This potential bias should be considered in the interpretation of OS. Therefore, PFS, rather than OS, was selected as a primary endpoint in this study. Third, radiological images were also retrospectively reviewed for the assessment of tumor response. When tumor recurrence was detected, tracing back to previous follow-up images was performed to determine when tumor recurrence began. This process made TTP in this study shorter in many cases than the actual time point when additional treatment was begun. However, all the images were reviewed again by three independent radiologists; consequently, the risk of interpretation bias should have been minimized. Last, treatment modalities (cTACE *versus* DEB-TACE) might have affected the early detection of local tumor recurrence on CT imaging follow up. Highly attenuated lipiodol accumulation could create artifacts around the tumor on CT images that might have delayed the detection of local tumor progression in the cTACE group. However, it could not change the outcome of this study because the cumulative probability of local recurrence in the cTACE group remained significantly lower than in the DEB-TACE group even at 5-year follow up.

In conclusion, DEB-TACE is followed by significantly shorter PFS than cTACE in patients with nodular HCCs ($n \leqslant 5$) and Child–Pugh class A liver function, although OS is comparable. Postembolization syndrome occurs more frequently in the cTACE group than in the DEB-TACE group.

## Conflict of interest statement
The authors disclose the following: Dr. Yoon Jun Kim reports research grant from BTG, Bayer HealthCare Pharmaceuticals, Ono, AstraZeneca, Roche, LG Life Science, and Bristol-Myers Squibb, lecture fees from Bayer HealthCare Pharmaceuticals and Gilead Science, and serving as an advisory board member or consultant of Gilead Science, Bayer HealthCare Pharmaceuticals, Ono, and AbbVie; Dr. Jung-Hwan Yoon reports research grants from Bayer HealthCare Pharmaceuticals and AstraZeneca; Dr. Saebeom Hur reports research grants from Guerbet; and Dr. Jin Wook Chung reports grants and lecture fees from Guerbet and BTG; Dr. In Joon Lee, Dr. Jeong-Hoon Lee, Dr. Yun Bin Lee, Dr. Hwan Jun Jae, Dr. Myungsu Lee, Hyo-Cheol Kim, and Yong Hu Yin report no conflicts of interest.

## ORCID iDs
In Joon Lee   https://orcid.org/0000-0002-5779-5153

Jin Wook Chung   https://orcid.org/0000-0002-1090-6872

## Supplemental material
Supplemental material for this article is available online.

## References
1. Lencioni R, de Baere T, Soulen MC, *et al.* Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. *Hepatology* 2016; 64: 106–116.

2. Marrero JA, Kulik LM, Sirlin CB, *et al.* Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of liver diseases. *Hepatology* 2018; 68: 723–750.

3. Korean Liver Cancer Study Group and National Cancer Center Korea. 2014 Korean Liver Cancer Study Group-National Cancer Center Korea practice guideline for the management of hepatocellular carcinoma. *Korean J Radiol* 2015; 16: 465–522.

4. European Association for the Study of the Liver and European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; 69: 182–236.

5. Park JW, Chen M, Colombo M, *et al.* Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; 35: 2155–2166.

6. Golfieri R, Renzulli M, Mosconi C, *et al.* Hepatocellular carcinoma responding to superselective transarterial chemoembolization: an issue of nodule dimension? *J Vasc Interv Radiol* 2013; 24: 509–517.

7. Golfieri R, Cappelli A, Cucchetti A, *et al.* Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. *Hepatology* 2011; 53: 1580–1589.

8. Takaki S, Sakaguchi H, Anai H, *et al.* Long-term outcome of transcatheter subsegmental and segmental arterial chemoemobolization using lipiodol for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2012; 35: 544–554.

9. Orth RC, Wallace MJ, Kuo MD, *et al.* C-arm cone-beam CT: general principles and technical considerations for use in interventional radiology. *J Vasc Interv Radiol* 2008; 19: 814–820.

10. Pung L, Ahmad M, Mueller K, *et al.* The role of cone-beam CT in transcatheter arterial chemoembolization for hepatocellular carcinoma: a systematic review and meta-analysis. *J Vasc Interv Radiol* 2017; 28: 334–341.

11. Lee IJ, Chung JW, Yin YH, *et al.* Cone-beam computed tomography (CBCT) hepatic arteriography in chemoembolization for hepatocellular carcinoma: performance depicting tumors and tumor feeders. *Cardiovasc Intervent Radiol* 2015; 38: 1218–1230.

12. Varela M, Real MI, Burrel M, *et al.* Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007; 46: 474–481.

13. Johnson PJ, Kalayci C, Dobbs N, *et al.* Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocellular carcinoma: effect of coadministration of lipiodol. *J Hepatol* 1991; 13: 120–127.

14. de Baere T, Arai Y, Lencioni R, *et al.* Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. *Cardiovasc Intervent Radiol* 2016; 39: 334–343.

15. Hong K, Khwaja A, Liapi E, *et al.* New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. *Clin Cancer Res* 2006; 12: 2563–2567.

16. 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.

17. Vogl TJ, Lammer J, Lencioni R, *et al.* Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. *AJR Am J Roentgenol* 2011; 197: W562–570.

18. Golfieri R, Giampalma E, Renzulli M, *et al.* Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. *Br J Cancer* 2014; 111: 255–264.

19. Facciorusso A, Mariani L, Sposito C, *et al.* Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol* 2016; 31: 645–653.

20. Facciorusso A, Di Maso M and Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: a meta-analysis. *Dig Liver Dis* 2016; 48: 571–577.

21. Xie ZB, Wang XB, Peng YC, *et al.* Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. *Hepatol Res* 2015; 45: 190–200.

22. Chen P, Yuan P, Chen B, *et al.* Evaluation of drug-eluting beads versus conventional transcatheter arterial chemoembolization in patients with unresectable hepatocellular

carcinoma: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2017; 41: 75–85.

23. Ueno S, Tanabe G, Nuruki K, *et al*. Prognostic performance of the new classification of primary liver cancer of Japan (4th edition) for patients with hepatocellular carcinoma: a validation analysis. *Hepatol Res* 2002; 24: 395–403.

24. Choi JW, Chung JW, Lee DH, *et al*. Portal hypertension is associated with poor outcome of transarterial chemoembolization in patients with hepatocellular carcinoma. *Eur Radiol* 2018; 28: 2184–2193.

25. Lee IJ, Chung JW, Yin YH, *et al*. Cone-beam CT hepatic arteriography in chemoembolization for hepatocellular carcinoma: angiographic image quality and its determining factors. *J Vasc Interv Radiol* 2014; 25: 1369–1379; quiz 1379- e1361.

26. Lencioni R and Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; 30: 52–60.

27. National Cancer Institute PROCSG. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf, 2017.

28. Leung DA, Goin JE, Sickles C, *et al*. Determinants of postembolization syndrome after hepatic chemoembolization. *J Vasc Interv Radiol* 2001; 12: 321–326.

29. Kan Z, Ivancev K, Hagerstrand I, *et al*. In vivo microscopy of the liver after injection of Lipiodol into the hepatic artery and portal vein in the rat. *Acta Radiol* 1989; 30: 419–425.

30. Kan Z, Sato M, Ivancev K, *et al*. Distribution and effect of iodized poppyseed oil in the liver after hepatic artery embolization: experimental study in several animal species. *Radiology* 1993; 186: 861–866.

31. Kitao A, Zen Y, Matsui O, *et al*. Hepatocarcinogenesis: multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography–radiologic-pathologic correlation. *Radiology* 2009; 252: 605–614.

32. Miyayama S, Matsui O, Yamashiro M, *et al*. Ultraselective transcatheter arterial chemoembolization with a 2-f tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. *J Vasc Interv Radiol* 2007; 18: 365–376.

33. Irie T, Kuramochi M and Takahashi N. Diameter of main tumor feeding artery of a hepatocellular carcinoma: measurement at the entry site into the nodule. *Hepatol Res* 2016; 46: E100–104.

34. Matsui O, Kobayashi S, Sanada J, *et al*. Hepatocelluar nodules in liver cirrhosis: hemodynamic evaluation (angiography-assisted CT) with special reference to multi-step hepatocarcinogenesis. *Abdom Imaging* 2011; 36: 264–272.

35. Iwamoto S, Yamaguchi T, Hongo O, *et al*. Excellent outcomes with angiographic subsegmentectomy in the treatment of typical hepatocellular carcinoma: a retrospective study of local recurrence and long-term survival rates in 120 patients with hepatocellular carcinoma. *Cancer* 2010; 116: 393–399.

36. Namur J, Citron SJ, Sellers MT, *et al*. Embolization of hepatocellular carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants. *J Hepatol* 2011; 55: 1332–1338.

37. Richter G, Radeleff B, Stroszczynski C, *et al*. Safety and feasibility of chemoembolization with doxorubicin-loaded small calibrated microspheres in patients with hepatocellular carcinoma: results of the MIRACLE I prospective multicenter study. *Cardiovasc Intervent Radiol*. Epub ahead of print 22 November 2017. DOI: 10.1007/s00270-017-1839-2.

38. Aliberti C, Carandina R, Lonardi S, *et al*. Transarterial chemoembolization with small drug-eluting beads in patients with hepatocellular carcinoma: experience from a cohort of 421 patients at an Italian center. *J Vasc Interv Radiol* 2017; 28: 1495–1502.

39. Yoshida K, Matsui O, Miyayama S, *et al*. Isolated arteries originating from the intrahepatic arteries: anatomy, function, and importance in intervention. *J Vasc Interv Radiol* 2018; 29: 531–537 e531.

40. 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.