



Prospective Multi-Center Korean Registry of Transcatheter Arterial Chemoembolization with Drug-Eluting Embolics for Nodular Hepatocellular Carcinoma: A Two-Year Outcome Analysis

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Objective: To assess the two-year treatment outcomes of chemoembolization with drug-eluting embolics (DEE) for nodular hepatocellular carcinoma (HCC).

Materials and Methods: This study was a prospective, multicenter, registry-based, single-arm trial conducted at five university hospitals in Korea. Patients were recruited between May 2011 and April 2013, with a target population of 200. A DC Bead loaded with doxorubicin was used as the DEE agent. Patients were followed up for two years. Per-patient and per-lesion tumor response analysis, per-patient overall survival (OS) and progression-free survival (PFS) analysis, and per-lesion tumor control analysis were performed.

Results: The final study population included 152 patients, with 207 target lesions for the per-lesion analysis. At one-month, six-month, one-year, and two-year per-patient assessments, complete response (CR) rates were 40.1%, 43.0%, 33.3%, and 19.6%, respectively. The objective response (OR) rates were 91.4%, 55.4%, 35.1%, and 19.6%, respectively. The cumulative two-year OS rate was 79.7%. The cumulative two-year PFS rate was 22.4% and the median survival was 9.3 months. In multivariable analysis, the Child-Pugh score ($p = 0.019$) was an independent predictor of OS, and tumor multiplicity ($p < 0.001$), tumor size ($p = 0.020$), and Child-Pugh score ($p = 0.006$) were independent predictors of PFS. In per-lesion analysis, one-month, six-month, one-year and two-year CR rates were 57.5%, 58.5%, 45.2%, and 33.3%, respectively, and the OR rates were 84.1%, 65.2%, 46.6%, and 33.3%, respectively. The cumulative two-year per-lesion tumor control rate was 36.2%, and the median time was 14.1 months. The Child-Pugh score ($p < 0.001$) was the only independent predictor of tumor control. Serious adverse events were reported in 11 patients (7.2%).

Conclusion: DEE chemoembolization for nodular HCCs in the Korean population showed acceptable survival, tumor response, and safety profiles after a two-year follow-up. Good liver function (Child-Pugh score A5) was a key predictor of per-patient OS, PFS, and per-lesion tumor control.

Keywords: Hepatocellular carcinoma; Chemoembolization; Drug-eluting embolics; Drug-eluting beads

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INTRODUCTION

Chemoembolization has shown survival benefits in randomized controlled trials and is the most commonly chosen palliative option worldwide for the treatment of patients with hepatocellular carcinoma (HCC) [1-3]. However, the heterogeneity of this technique is considered a drawback for treatment [4,5]. Chemoembolization with drug-eluting embolics (DEE) was developed as an alternative to chemoembolization with ethiodized oil [6]. The technique is characterized by embolization with calibrated microspheres and the release of chemotherapeutic agents taken up by the microspheres in a more controlled manner over a longer period compared to the conventional technique [6-8]. This helps maximize the locoregional effect and minimize systemic adverse effects.

Preclinical and early clinical studies on chemoembolization with DEE were carried out to prove this concept and reported good safety profiles [7-10]. Most of the prospective clinical studies showed that chemoembolization with DEE had better or comparable tolerability compared with conventional chemoembolization or bland embolization. However, it failed to show superiority in patient survival rates or treatment response, and conflicting results were reported regarding

its efficacy [11-17]. We present two-year outcomes from a prospective multicenter registry-based trial on DEE chemoembolization in patients with nodular HCC in Korea. The primary purpose of this study was to assess patient survival and tumor response.

MATERIALS AND METHODS

This study was a prospective multicenter registry-based single-arm clinical trial performed at five university hospitals in Korea. The target patient population was 200, and patients were recruited from May 2011 to April 2013. The key inclusion and exclusion criteria are listed in Table 1. Institutional Review Board approval was obtained before the initiation of the study at each institution, and informed consent was obtained from all patients. The study was registered at ClinicalTrials.gov (ID code NCT01332669).

DEE Chemoembolization Procedure

Details of the DEE chemoembolization procedure were described in our previous report on the six-month outcome of this registry [18]. A vial of DEE (DC Bead, Biocompatibles UK) loaded with 70–75 mg of doxorubicin (Adriamycin, Ildong Pharmaceutical) was used. For a standard procedure,

Table 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Clinical or histological diagnosis of HCC (AASLD criteria)	• Gross vascular invasion, bile duct invasion or extrahepatic metastasis on CT or MRI
• Single nodular or multinodular HCC with at least one hypervascular measurable lesion on dynamic CT or MRI	• Tumor burden involving > 50% of the liver
• Not suitable for curative treatments or rejects such treatments	• History of anti-cancer therapy for HCC, except hepatic resection performed more than a year earlier from registry
• ECOG performance status 0 or 1	• History of HCC rupture
• Child-Pugh score A5, A6 or B7	• History of biliary tract repair or endoscopic biliary treatment
• Laboratory criteria (within 2 weeks)	• Refractory ascites or pleural fluid
- White blood cell count > 3000/mm ³	• Contraindications for hepatic embolization (hepatofugal blood flow, arteriovenous shunt)
- Platelet count > 5 x 10 ⁴ /mm ³	• Hypersensitivity to doxorubicin
- Serum bilirubin level < 3.0 mg/dL	• Contrast media allergy contraindicating angiography
- Serum AST and ALT level < 5-times of upper limit of normal	• Acute or active diseases including refractory heart failure, angina pectoris or arrhythmia
- Serum creatinine level < 1.5 mg/dL	• Myocardial infarction within 6 months
- Hemoglobin level > 8.0 g/dL	• Chronic renal failure or end-stage renal disease
	• Active bacterial or fungal infection
	• Active hemorrhage of digestive system
	• Uncontrolled other malignancies

AASLD = American Association for the Study of Liver Diseases, ALT = alanine transaminase, AST = aspartate transaminase, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma

embolics of 100–300 μm in size were recommended. However, the choices of the actual amount of doxorubicin and embolic size were determined by operators considering specific patient and tumor characteristics. A superselective (segmental or subsegmental) approach was used whenever possible by using a small-bore microcatheter (2.0 to 2.4-Fr). The recommended embolization endpoint was near stasis (the contrast column was clear within 2–5 heartbeats on the completion angiography). A treatment cycle consisted of different numbers of treatment sessions that required to cover all the viable tumors. Up to two vials of DEE were allowed for each session. In patients with a large tumor burden in whom two vials of DEE were insufficient, a separate split session was recommended at a two- to four-week interval to complete the cycle.

Follow-Up Imaging and Repeated Procedures

Regular clinical follow-up was performed using laboratory and imaging studies. Tumor response assessment was performed with dynamic contrast-enhanced CT or MRI at one, three, and six months after the procedure and at three-month intervals thereafter. Repeated cycles of DEE chemoembolization were recommended in on-demand settings when there was a viable tumor on follow-up imaging. Conversion to other treatments or supportive care was permitted in the following situations: progressive disease (PD), failure to achieve objective response (OR) in the targeted tumor after at least two cycles of DEE chemoembolization, or clinical deterioration of the patient in terms of performance status or persistent hepatic decompensation.

Data Analysis

All the data were reviewed by three independent reviewers who did not participate in the trial execution.

The tumor response and survival assessment in this study consisted of two separate approaches: per-patient and per-lesion analyses. Per-patient tumor response was determined using the modified Response Evaluation Criteria in Solid Tumors on CT or MRI [19]. Two representative tumors were selected as target lesions, and the others were classified as non-target lesions. Target lesions were selected based on their size (longer diameter) and suitability for repeated measurements. The overall response was determined by the change in the sum of the maximum diameter of the viable portion in target lesions, the overall change in non-target lesions, and the presence of new lesions. The overall

response was classified as complete response (CR), partial response (PR), stable disease (SD), or PD. The OR was defined as CR plus PR. When PD was present, the cause of progression was categorized as local tumor progression (LTP), intrahepatic distant recurrence (IDR), gross vascular invasion (VI), or extrahepatic distant metastasis (EDM). The responses of individual target lesions were analyzed in a per-lesion assessment. The same concepts and criteria were applied, and the response was determined as CR, PR, SD, PD, and OR based on the diameter change of the viable portion in each target lesion. Per-patient tumor response assessment was performed until the patient reached PD, or when the patient expired, was lost to follow-up, was referred to another institution, or underwent additional treatment other than DEE chemoembolization. In per-lesion assessment, the same strategy was used, but the assessment was stopped only when the imaging study was no longer available, when the target lesion was in PD status, or when it was targeted by other treatment modalities, regardless of patient status. In the per-patient survival analysis, overall survival (OS), progression-free survival (PFS), and LTP-free survival were assessed. Patients who underwent liver transplantation during follow-up were excluded from the survival analysis at the time of surgery. For per-lesion analysis, per-lesion tumor control was assessed to determine the outcome of the target lesions. In this analysis, the event was defined as PD on a per-lesion tumor response assessment.

Safety

For the two-year follow-up period, all medical events that were considered to be related to the procedure and the disease were recorded, including any symptoms or signs presented by the patient. During the post-procedure hospital stay, the presence of post-embolization syndrome (PES) was assessed. For hepatic complication assessment, clinical medical records and liver follow-up imaging studies were reviewed and searched for findings on the liver abscess, bile duct dilation, biloma, portal vein thrombosis, and liver infarction. Bile duct injury was defined as prominent when bile duct dilatation was observed in a segmental or wider distribution. Serious adverse events (SAEs) were defined as any event resulting in death, any immediate life-threatening condition, unscheduled hospital visits, prolonged hospitalization, permanent or significant disability, or incapacity. Prolonged hospitalization was defined as a length of stay longer than seven days.

Statistical Analysis

For per-patient tumor response assessment, patients were stratified by demographic and procedural variables. For per-lesion assessment, the target lesions were stratified by size. Their statistical significance was tested using the chi-squared test, Fisher's exact test, or chi-squared test for trend. Subsequently, univariable and multivariable logistic regression analyses were performed. The OS, PFS, and LTP-free survival rates were analyzed using the same stratification variables. Kaplan-Meier survival analysis with a log-rank test was performed, and subsequent analysis with the Cox proportional hazards model was applied. To determine the correlation between per-lesion tumor response and demographic characteristics, the per-lesion tumor control rate of the target lesion was analyzed using Kaplan-Meier survival analysis with a log-rank test and Cox proportional hazards model. $p < 0.05$ was defined as statistically significant in all tests, and variables with $p < 0.10$, in univariable analysis, were selected for multivariable regression analysis. Commercially available statistical packages were used (SPSS 22, IBM Corp.; MedCalc, version 16.8, MedCalc Software).

RESULTS

Patients

Of the 200 registered patients, 48 were excluded from the analysis on central review as they did not meet all the inclusion criteria. The final study population was 152. The baseline characteristics of the patients are summarized in Table 2. The mean patient age was 61.4 years (range, 34–86 years), and 82.2% were male. Most of the patients were in the Child-Pugh class A ($n = 143$, 94.1%). A total of 84 (55.3%) patients had a single tumor, and 68 (44.7%) patients had multiple tumors. There were 11 (7.2%), 77 (50.7%), 26 (17.1%), and 38 (25.0%) patients with Barcelona Clinic Liver Cancer (BCLC) stages 0, A, B, and C, respectively.

There were 207 target tumors for per-lesion analysis, with a mean and median size of 3.2 cm (standard deviation: 2.1 cm) and 2.5 cm (interquartile range: 1.7–3.6 cm), respectively. There were 63 tumors (30.4%) smaller than 2 cm, 113 (54.6%) between 2–5 cm in size, and 31 (15.0%) larger than 5 cm.

DEE Chemoembolization and Adjunctive Procedures

In the first DEE chemoembolization, DEE of 100–300 μm in size was used in 145 (95.4%) patients, and DEE of 300–500

Table 2. Baseline Characteristics of 152 Patients

Variable	Value
Sex	
Male	125 (82.2)
Female	27 (17.8)
Age, year*	61.4 \pm 10.1
Cause of chronic liver disease	
HBV	103 (67.8)
HCV	26 (17.1)
HBV + HCV	5 (3.3)
Non-viral	18 (11.8)
History of surgical HCC treatment	4 (2.6)
History of other malignancies	11 (7.2)
Child-Pugh score	
A5	105 (69.1)
A6	38 (25.0)
B7	9 (5.9)
ECOG performance status	
0	114 (75.0)
1	38 (25.0)
Maximum tumor diameter, cm [†]	3.6 \pm 2.2; 3.0 (2.2–4.5)
Sum of target lesion diameters, cm [†]	5.5 \pm 7.0; 3.8 (2.6–5.9)
Number of tumors	
Single, cm	84 (55.3)
< 2	18 (11.8)
2–5	51 (33.6)
> 5	15 (9.9)
Multiple	68 (44.7)
Within Milan criteria	34 (22.4)
Beyond Milan criteria	34 (22.4)
Bilobar disease	43 (28.3)
BCLC stage [‡]	
0	11 (7.2)
A	77 (50.7)
B	26 (17.1)
C	38 (25.0)
Okuda stage	
I	135 (88.8)
II	17 (11.2)
Modified UICC stage	
I	18 (11.8)
II	78 (51.3)
III	56 (36.8)
Alpha fetoprotein level, ng/mL [†]	1100.7 \pm 4573.7; 17.3 (6.1–159.4)
≤ 20	78 (51.3)
> 20, ≤ 400	48 (31.6)
> 400	26 (17.1)

Values are number of patients and lesions with the percentage in parentheses unless specified otherwise. *Values are mean \pm SD, [†]Values are mean \pm SD; and median with interquartile range in parentheses, [‡]BCLC stage A included all the patients with single tumor regardless of its size. BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, HCV = hepatitis C virus, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, SD = standard deviation, UICC = Union for International Cancer Control

μm in size was used in seven patients (4.6%). The delivered DEE amount was 1.02 ± 0.80 , and the doxorubicin amount was 68.41 ± 53.88 mg. Additional bland embolization was performed in 27 (17.8%) patients because of the persistent vascular lake phenomenon after DEE delivery [20]. The embolic material for bland embolization was gelatin sponge particles in 18 patients, polyvinyl alcohol particles in seven patients, bland DC beads in one patient, and a mixture of N-butyl-2-cyanoacrylate and ethiodized oil in one patient. Extrahepatic collateral treatment was performed with DEE in seven (4.6%) patients and split treatment was performed in seven (4.6%) patients. The second cycle treatment was performed in 69 (45.4%) patients, the third cycle in 20 (13.2%) patients, the fourth cycle in three (2.0%) patients, and the fifth cycle in one (0.7%) patients. During the 245 cycles of treatment, extrahepatic collateral treatment was performed in 25 (10.2%) patients.

During the two-year follow-up, the tumor response assessment protocol was terminated in 127 (83.6%) patients. The protocol was terminated due to PD in 82 patients (64.6%). The remaining 45 (35.4%) patients were in a non-PD status, and the protocol was terminated for other reasons. The details of the tumor responses and clinical situations at the time of protocol termination are shown in Table 3. A total of 104 (81.9%) patients (74 [71.2%] in PD status and 30 [28.8%] in non-PD status) underwent additional treatment other than DEE chemoembolization. The most commonly chosen modality was conventional chemoembolization ($n = 66$, 63.5%). After conversion to second-line treatment, 77 patients underwent 159 cycles of conventional chemoembolization (1–7 cycles per patient). Forty patients underwent 47 cycles of radiofrequency ablation (1–3 cycles per patient), 15 patients underwent 20 cycles of external beam radiation

Table 3. Tumor Response and Clinical Situation at the Time of the Tumor Response Assessment Protocol Termination in 127 Patients

	Tumor Response Overall	CR	PR	SD	Non-PD	PD
All	127	9 (7.1)	33 (26.0)	3 (2.4)	45 (35.4)	82 (64.6)
Death	3 (2.4)	2 (22.2)	1 (3.0)		3 (6.7)	
Follow-up loss or transfer	20 (15.7)	3 (33.3)	8 (24.2)	1 (33.3)	12 (26.7)	8 (9.8)
Other treatment	104 (81.9)	4 (44.4)	24 (72.7)	2 (66.7)	30 (66.7)	74 (90.2)
Conventional chemoembolization	66 (52.0)	1 (11.1)	12 (36.4)	1 (33.3)	14 (31.1)	52 (63.4)
+ Combination treatment	4 (3.1)	1 (11.1)	1 (3.0)		2 (4.4)	2 (2.4)
Radiofrequency ablation	23 (18.1)	1 (11.1)	9 (27.3)		10 (22.2)	13 (15.9)
Percutaneous ethanol injection	6 (4.7)		2 (6.1)		2 (4.4)	4 (4.9)
Liver transplantation	4 (3.2)	1 (11.1)			1 (2.2)	3 (3.7)
Resection	3 (2.4)	1 (11.1)	1 (3.0)	1 (33.3)	3 (6.7)	
Intraarterial chemotherapy	2 (1.6)					2 (2.4)

Values are number of patients with the percentage in parentheses. CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease

Table 4. Tumor Responses

	Numbers at Risk	CR	PR	SD	PD	OR
Per-patient						
1 month	152	61 (40.1)	78 (51.3)	10 (6.6)	3 (2.0)	139 (91.4)
6 month	121	52 (43.0)	15 (9.9)	1 (0.8)	53 (43.8)	67 (55.4)
1 year	111	37 (33.3)	2 (1.8)	1 (0.9)	71 (64.0)	39 (35.1)
2 year	107	21 (19.6)	0 (0)	0 (0)	86 (80.4)	21 (19.6)
Per-lesion						
1 month	207	119 (57.5)	55 (26.6)	32 (15.5)	1 (0.5)	174 (84.1)
6 month	164	96 (58.5)	11 (67.1)	7 (4.3)	50 (30.5)	107 (65.2)
1 year	146	66 (45.2)	2 (1.4)	2 (1.4)	76 (52.1)	68 (46.6)
2 year	141	47 (33.3)	0 (0)	0 (0)	94 (66.7)	47 (33.3)

Values are number of patients with the percentage in parentheses. CR = complete response, OR = objective response, PD = progressive disease, PR = partial response, SD = stable disease

Table 5. Stratified Results of Tumor Response and Survival 2 Year and Analysis of Median Survival

Subgroup	Numbers at Risk	CR (%)	PD (%)	Cumulative PFS Rate (%)	Median PFS (Months)	Cumulative LTP Free Survival Rate (%)	Median LTP Free Survival (Months)	Cumulative OS Rate (%)
Child-Pugh score A5 vs. A6-B7								
A5	73	18 (24.7)	55 (75.3)	27.2	12.0	35.8	16.8	84.7
A6 or B7	34	3 (8.8)	31 (91.2)	11.2	6.4	11.9	7.0	67.9
<i>p</i> value		0.055	0.055	0.004		0.001		0.015
Tumor multiplicity								
Single	60	20 (33.3)	40 (66.7)	35.1	16.8	37.8	16.9	84.7
Multiple	47	1 (2.1)	46 (97.9)	3.3	6.8	15.2	7.8	73.7
<i>p</i> value		< 0.001	< 0.001	< 0.001		0.003		0.120
Single tumor, cm								
< 2	16	6 (37.5)	10 (62.5)	40.5	9.4	40.5	11.6	81.3
2-5	35	12 (34.3)	23 (65.7)	33.7	16.8	38.0	16.9	87.9
> 5	9	2 (22.2)	7 (77.8)	30.6	8.4	33.7	18.3	78.6
<i>p</i> value		0.726	0.726	0.636		0.714		0.467
Multiple tumors								
Within Milan	24	1 (4.2)	23 (95.8)	5.7	9.3	24.0	10.8	75.8
Beyond Milan	23	0 (0)	23 (100)	0	4.2	0	4.8	71.2
<i>p</i> value		1.000	1.000	< 0.001		0.003		0.869
Tumor distribution								
Unilobar	77	19 (24.7)	58 (75.3)	28.1	10.6	30.8	12.3	83.2
Bilobar	30	2 (6.7)	28 (93.3)	5.2	7.0	20.6	8.4	70.6
<i>p</i> value		0.035	0.035	0.010		0.296		0.105
BCLC stage*								
0	10	4 (40.0)	6 (60.0)	40.4	23.1	40.4	23.1	100
A	55	13 (23.6)	42 (76.4)	26.5	13.1	36.5	14.8	84.2
B	16	0 (0)	16 (100)	0	4.2	0	5.8	67.4
C	26	4 (15.4)	22 (84.6)	15.8	7.3	15.9	8.7	71.2
<i>p</i> value		0.062 [†]	0.062 [†]	< 0.001		0.001		0.123
Okuda stage								
I	95	21 (22.1)	74 (77.9)	24.8	10.6	32.1	13.1	81.8
II	12	0 (0)	12 (100)	0	8.0	0	8.0	61.4
<i>p</i> value		0.118 [‡]	0.118 [‡]	0.053		0.006		0.130
Modified UICC stage								
I	16	6 (37.5)	10 (62.5)	40.5	9.4	40.5	11.6	81.3
II	52	15 (28.8)	37 (71.2)	32.3	14.8	34.1	14.8	83.7
III	39	0 (0)	39 (100)	0	6.0	14.3	7.0	73.9
<i>p</i> value		< 0.001	< 0.001	< 0.001		0.024		0.444

Table 5. Stratified Results of Tumor Response and Survival 2 Year and Analysis of Median Survival (Continued)

Subgroup	Numbers at Risk	CR (%)	PD (%)	Cumulative PFS Rate (%)	Median PFS (Months)	Cumulative LTP Free Survival Rate (%)	Median LTP Free Survival (Months)	Cumulative OS Rate (%)
Alpha fetoprotein level, ng/mL								
≤ 20	53	14 (26.4)	39 (73.6)	31.9	10.8	34.6	11.6	82.6
> 20, ≤ 400	36	5 (13.9)	31 (86.1)	15.0	9.0	26.7	14.8	82.0
> 400	18	2 (11.1)	16 (88.9)	9.7	6.8	11.4	7.1	66.0
<i>p</i> value		0.209	0.209	0.185		0.324		0.266
Subgroup	Numbers at Risk	CR (%)	PD (%)	Cumulative Tumor Control Rate (%)	Median Tumor Control Time (Months)			
Tumor size, per-lesion, n = 207, cm								
< 2	141	47 (33.3)	94 (66.7)	36.2	14.1			
2-5	46	12 (26.1)	34 (73.9)	29.5	11.4			
> 5	78	32 (41.0)	46 (59.0)	42.2	17.7			
<i>p</i> value		0.080	0.080	0.125				

*BCLC stage A included all the patients with single tumor regardless of its size, †Chi-squared test for trend, ‡Fisher's exact test. BCLC = Barcelona Clinic Liver Cancer, CR = complete response, LTP = local tumor progression, PD = progressive disease, PFS = progression-free survival, UICC = Union for International Cancer Control

therapy, nine patients underwent 10 cycles of percutaneous ethanol injection, and three patients underwent five cycles of intra-arterial chemotherapy. A total of nine and five patients underwent living-donor liver transplantation and resection, respectively. Ten patients received systemic chemotherapy, including sorafenib, in nine patients.

Tumor Response and Survival Analysis

The results of the two-year tumor response and survival analyses are summarized in Tables 4 and 5. Patients who were still undergoing DEE treatment and those for whom the protocol was terminated due to PD were included in the tumor response assessment. At the one-month, six-month, one-year and two-year assessments, the CR rates were 40.1%, 43.0%, 33.3%, and 19.6%, respectively, and the OR rates were 91.4%, 55.4%, 35.1%, and 19.6%, respectively. The most common cause of PD was LTP in 52 patients (60.5%). The cause was IDR in 19 (22.1%) patients, IDR and LTP in 14 (16.3%) patients, and LTP, VI, and EDM in one (1.2%) patient. On multivariable logistic regression analysis, tumor multiplicity was the only independent predictor of CR at two years ($p = 0.003$).

The results of the survival analysis are shown in Figure 1. The cumulative two-year OS rate was 79.7%, and the Child-Pugh score ($p = 0.019$) was the only independent predictor in the multivariable analysis. The results of the stratified analysis are shown in Figure 2. The cumulative two-year PFS rate was 22.4% and the median survival was 9.3 months, and tumor multiplicity ($p < 0.001$), tumor size ($p = 0.020$), and Child-Pugh score ($p = 0.006$) were independent predictors. The results of PFS analysis stratified by Child-Pugh score and tumor multiplicity are shown in Figure 3. The cumulative two-year LTP-free survival rate was 28.8% and the median survival was 11.5 months, and tumor multiplicity ($p = 0.007$) and Child-Pugh score ($p = 0.002$) were independent predictors. The results of LTP-free survival analysis stratified by Child-Pugh score and tumor multiplicity are shown in Figure 4.

In per-lesion analysis at one-month, six-month, one-year and two-year assessments, the CR rates were 57.5%, 58.5%, 45.2%, and 33.3%, respectively. The OR rates were 84.1%, 65.2%, 46.6%, and 33.3%, respectively (Table 4). The CR rate was significantly higher in patients with a Child-Pugh score of A5 than in A6/B7 patients (42.9% vs. 16.0%, $p = 0.001$). When stratified by tumor size, the CR rate tended to differ according to size, but this did not reach statistical significance (< 2 cm, 26.1%; 2-5 cm, 41.0%; > 5 cm,

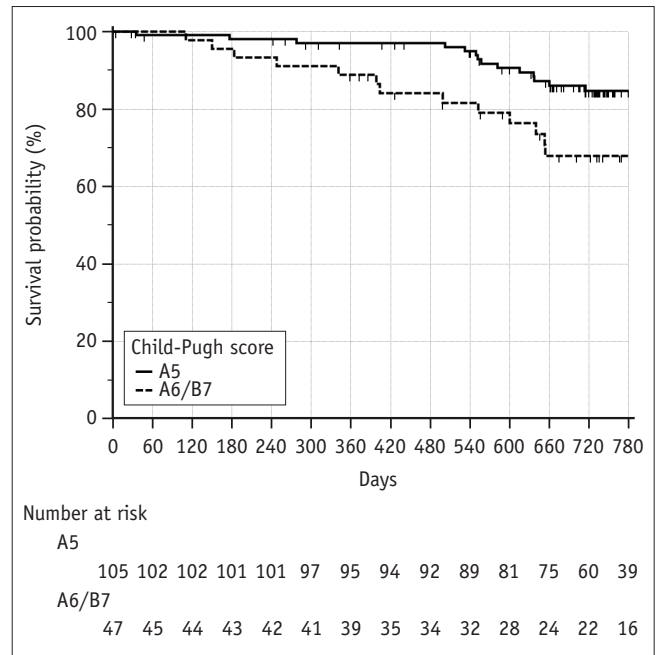
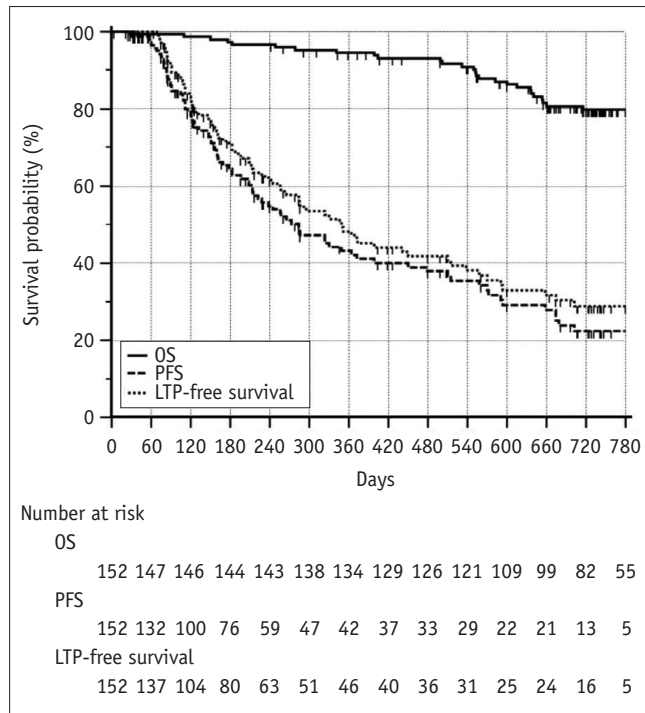


Fig. 1. Kaplan-Meier curve of per-patient survival analysis. The cumulative two-year OS rate was 79.7%. The cumulative two-year PFS rate was 22.4%, and the median survival was 9.3 months. The cumulative two-year LTP-free survival rate was 28.8%, and the median survival was 11.5 months. LTP = local tumor progression, OS = overall survival, PFS = progression-free survival

Fig. 2. Kaplan-Meier curve of OS subgroup analysis. The Child-Pugh score was the only independent predictor of OS ($p = 0.019$). The two-year OS rate was 84.7% in Child-Pugh score A5 patients and was 67.9% in A6/B7 patients. OS = overall survival

17.6%; $p = 0.080$). The cumulative two-year per-lesion tumor control rate was 36.2%, and the median time was 14.1 months (Fig. 5A). In multivariable analysis, the Child-Pugh score was the only independent predictor ($p < 0.001$), and the results of the stratified analysis are shown in Figure 5B. There was no significant difference in per-lesion tumor control by tumor size. However, tumors in the 2–5 cm group showed better tumor control than those in the other groups ($p = 0.125$) (Fig. 5C).

Safety

PES was reported after 164 of 245 treatment cycles (66.9%). SAEs were reported in 11 patients (7.2%). The causes were PES in five patients, biliary injury in four, a necessity for admission to control ascites in one, and cerebral infarction not related to disease or treatment in one. The prominent biliary injury was demonstrated on imaging in 30 patients (19.7%).

DISCUSSION

This study was a prospective study with a relatively large

patient population, and such investigations have seldom been performed in Asian countries. Results at one-year assessment showed CR and OR rates of 33.3% and 35.1%, respectively. These were comparable to previous reports with one-year CR rates of 20–48.9% and OR rates of 25.7–55.3% [11,21]. The cumulative two-year CR rate was 19.6%, and such a long-term response assessment has seldom been reported previously. The cumulative two-year PFS rate was 22.4%, with a median survival of 9.3 months in the current study, which was comparable to the previously reported median PFS or time-to-progression of 9–13 months [11,13,15,21,22]. The cumulative two-year OS rate of 79.7% was comparable to previous reports with 48–83.8% survival rates [11,13,14,23]. However, the outcomes of DEE chemoembolization for HCC are not suitable for head-to-head comparisons due to varying study designs and patient demographics.

As DEE chemoembolization is a palliative local treatment modality, local tumor control is considered an important marker of efficiency. To investigate the efficiency of individual target tumors, a detailed per-lesion tumor response assessment was performed in the current study. Several reports have documented local responses after DEE chemoembolization, but direct per-lesion analysis with extended follow-up has not been well reported [13,21].

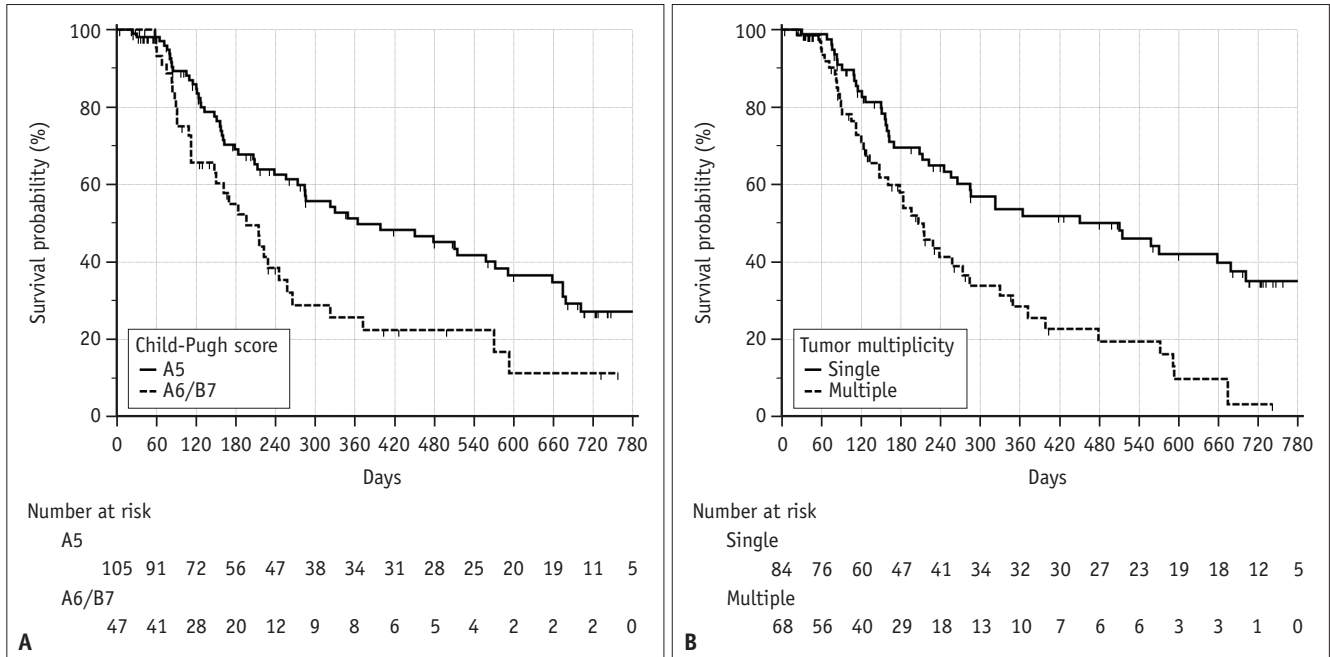


Fig. 3. Kaplan-Meier curve of PFS subgroup analysis. Child-Pugh score ($p = 0.006$), tumor multiplicity ($p < 0.001$), and tumor size ($p = 0.020$) were independent predictors of the PFS.

A. In Child-Pugh score A5 patients, the PFS rate at 2 year and median survival were 27.2% and 12.0 months, respectively, and in A6/B7 patients, they were 11.2% and 6.4 months, respectively. **B.** In patients with single tumors, the PFS rate at 2 year and median survival were 35.1% and 16.8 months, respectively, and in patients with multiple tumors, they were 3.3% and 6.8 months, respectively. PFS = progression-free survival

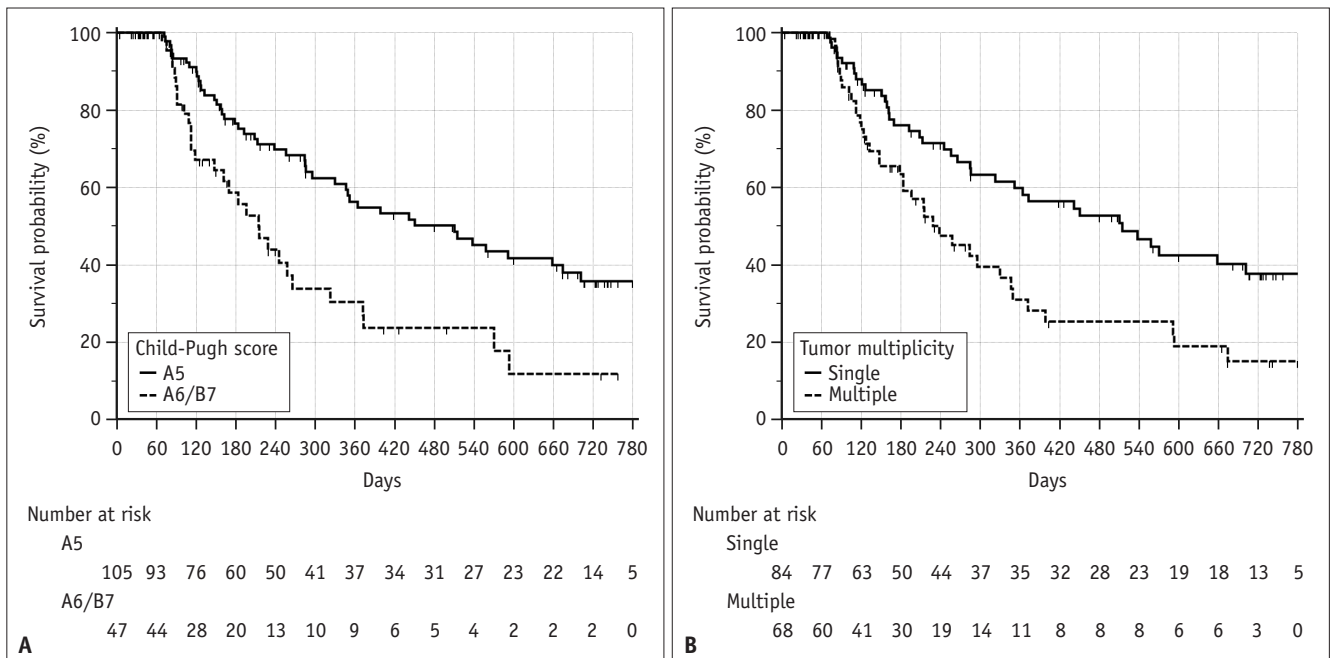


Fig. 4. Kaplan-Meier curve of LTP-free survival subgroup analysis. Child-Pugh score ($p = 0.002$) and tumor multiplicity ($p = 0.007$) were independent predictors of LTP-free survival.

A. In Child-Pugh score A5 patients, the LTP-free survival rate at 2 year and median survival were 35.8% and 16.8 months, respectively, and in A6/B7 patients, they were 11.9% and 7.0 months, respectively. **B.** In patients with single tumors, the LTP-free survival rate at 2 year and median survival were 37.8% and 16.9 months, respectively, and in patients with multiple tumors, they were 15.2% and 7.8 months, respectively. LTP = local tumor progression

Two-Year Multi-Center Outcome of TACE Using Drug-Eluting Embolics for HCC

The cumulative two-year per-lesion CR rate was 33.3%, the tumor control rate was 36.2%, and the median tumor control time was 14.1 months. As tumor size is an important factor that determines disease stage and prognosis, per-

lesion analysis with size stratification was conducted [2,24,25]. The results of this study with per-patient and per-lesion approaches with efforts to exclude the effects of subsequent additional treatments showed that there is a

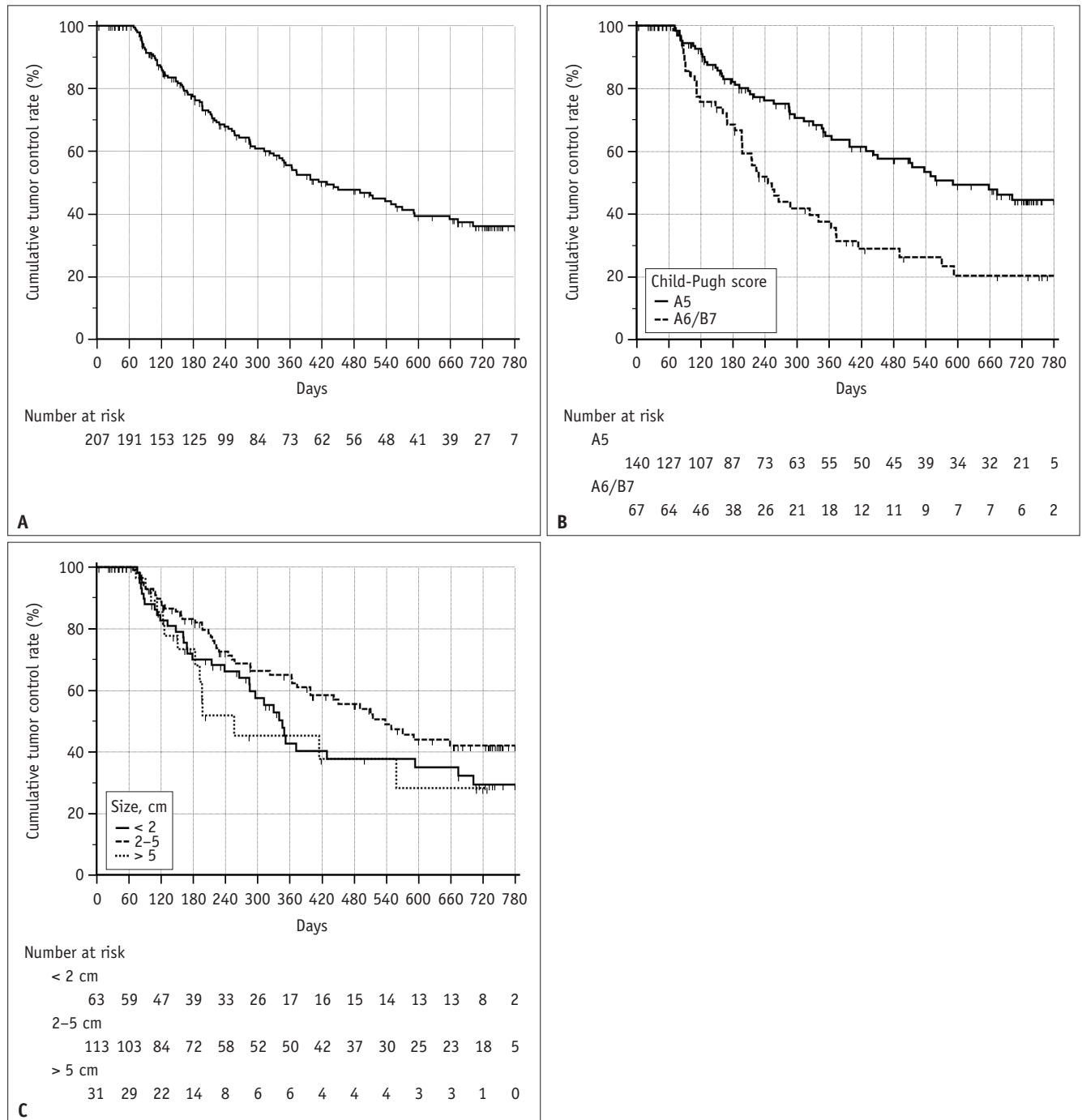


Fig. 5. Kaplan-Meier curve of per-lesion tumor control analysis.

A. The per-lesion tumor control rate was 36.2% at the two-year follow-up, and the median time was 14.1 months. The Child-Pugh score was the only independent predictor of per-lesion tumor control ($p < 0.001$). **B.** In Child-Pugh score A5 patients, per-lesion tumor control rate and median time were 44.5% and 19.4 months, respectively. In A6/B7 patients, they were 20.5% and 8.0 months, respectively. **C.** The target lesions 2–5 cm in size showed better tumor control than the others, without statistical significance ($p = 0.125$). The target lesions < 2, 2–5, and > 5 cm in size showed the per-lesion tumor control rate of 29.5%, 42.2%, and 28.4% and median time of 11.4, 17.7, and 8.4 months, respectively.

persistent deterioration of tumor response outcomes with longer follow-up, regardless of tumor size. These findings emphasize the importance of monitoring tumor response in the long term, even after reaching CR status. The tumor may remain stable for a while but can show progression after a longer follow-up period. There is another noteworthy finding in the per-lesion analysis with size stratification. The tumor response rate in tumors < 2 cm in size tended to be worse than that in larger ones, and this was beyond the usual expectation that smaller HCCs would have a better response to local treatment. A possible explanation is that DEE, due to its size and solid nature, cannot penetrate deeply into tiny tumor-supplying vessels in small tumors, and as a result, local outcomes are compromised.

The Child-Pugh score was one of the key predictors of tumor response and patient survival in the current study. Liver function is a well-known predictor of survival in patients with HCC and is also used in staging systems [24-26]. However, a correlation between liver function and tumor response after chemoembolization has seldom been reported. So far, there is no sufficient explanation for this finding. Recently, a study on the effect of clinically relevant portal hypertension on the outcomes after conventional chemoembolization concluded that portal hypertension is associated with early LTP and disease progression, as well as poor long-term survival [27]. The authors suggested peribiliary plexus hypertrophy, which develops with the progression of chronic liver disease [28], as a possible mechanism of poor local tumor control in patients with portal hypertension, as the structure can act as collateral blood supply channel after embolization. In addition, the authors suggested severe vessel tortuosity associated with advanced liver disease and liver shrinkage, which prohibits selective catheterization of tumor-supplying vessels, as another reason for poor local tumor control in patients with portal hypertension. This mechanism could explain the findings of the current study, even though the findings are not exactly the same, as the studies share a common background of advanced liver disease.

The major limitation of the current study is that approximately one-third of the patients were excluded from the tumor response protocol in non-PD status, two-thirds of which were due to receiving treatments other than DEE chemoembolization. This finding is consistent with the study design in which the choice and application of second-line treatment modality are not strictly controlled, with the ethical intention to not deprive patients of the opportunity

to receive tailored treatment. From the liberal study design, results from the current study may reflect the real-world practice pattern in Korea, where physicians usually utilize various local non-surgical treatment modalities when responses do not reach ideal expectations. However, the aforementioned poor local outcomes in small tumors might have affected this frequent modality conversion.

In summary, DEE chemoembolization for nodular HCCs in the Korean population seems effective and safe even after a two-year follow-up. Good liver function (Child-Pugh score A5) was an important prognostic factor for per-patient OS, PFS, and per-lesion tumor control.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jin Wook Chung. Data curation: Myungsu Lee, Jin Wook Chung, In Joon Lee, Saebeom Hur. Formal analysis: Myungsu Lee. Funding acquisition: Jin Wook Chung. Investigation: Jin Wook Chung, Kwang-Hun Lee, Jong Yun Won, Ho Jong Chun, Han Chu Lee, Jin Hyoung Kim, Hyo-Cheol Kim, Yoon Jun Kim, Gyoung Min Kim, Seung-Moon Joo, Jung Suk Oh. Methodology: Jin Wook Chung. Project administration: Jin Wook Chung. Resources: Myungsu Lee, Jin Wook Chung, In Joon Lee, Saebeom Hur. Supervision: Jin Wook Chung. Validation: Myungsu Lee, Jin Wook Chung. Visualization: Myungsu Lee, Jin Wook Chung. Writing—original draft: Myungsu Lee, Jin Wook Chung. Writing—review & editing: Myungsu Lee, Jin Wook Chung.

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REFERENCES

- Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-1739
- Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164-1171
- Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015;35:2155-2166
- Idée JM, Guiu B. Use of lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: a review. *Crit Rev Oncol Hematol* 2013;88:530-549
- Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;30:6-25
- Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. *J Vasc Interv Radiol* 2006;17:335-342
- Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. 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
- Lewis AL, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. *J Vasc Interv Radiol* 2006;17:1335-1343
- Varela M, Real MI, Burrell M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007;46:474-481
- Poon RT, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. *Clin Gastroenterol Hepatol* 2007;5:1100-1108
- Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. *Br J Cancer* 2014;111:255-264
- Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, 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
- Sacco R, Bargellini I, Bertini M, Bozzi E, Romano A, Petruzzi P, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 2011;22:1545-1552
- Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocellular carcinoma (HCC). *J Surg Oncol* 2010;101:476-480
- Song MJ, Chun HJ, Song DS, Kim HY, Yoo SH, Park CH, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol* 2012;57:1244-1250
- Liu YS, Ou MC, Tsai YS, Lin XZ, Wang CK, Tsai HM, et al. Transarterial chemoembolization using gelatin sponges or microspheres plus lipiodol-doxorubicin versus doxorubicin-loaded beads for the treatment of hepatocellular carcinoma. *Korean J Radiol* 2015;16:125-132
- Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol* 2016;34:2046-2053
- Lee M, Chung JW, Lee KH, Won JY, Chun HJ, Lee HC, et al. Korean multicenter registry of transcatheter arterial chemoembolization with drug-eluting embolic agents for nodular hepatocellular carcinomas: six-month outcome analysis. *J Vasc Interv Radiol* 2017;28:502-512
- Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60
- Seki A, Hori S, Shimono C. Management of vascular lake phenomenon on angiography during chemoembolization with superabsorbent polymer microspheres. *Jpn J Radiol* 2015;33:741-748
- Malagari K, Pomoni M, Kelekis A, Pomoni A, Dourakis S, Spyridopoulos T, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland

- embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2010;33:541-551
22. Martin RC 2nd, Rustein L, Pérez Enguix D, Palmero J, Carneiro V, Urbano J, et al. Hepatic arterial infusion of doxorubicin-loaded microsphere for treatment of hepatocellular cancer: a multi-institutional registry. *J Am Coll Surg* 2011;213:493-500
23. Malagari K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefanidou A, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. *Cardiovasc Intervent Radiol* 2012;35:1119-1128
24. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010;30:61-74
25. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* 2014;146:1691-1700.e3
26. The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 1998;28:751-755
27. Choi JW, Chung JW, Lee DH, Kim HC, Hur S, Lee M, et al. Portal hypertension is associated with poor outcome of transarterial chemoembolization in patients with hepatocellular carcinoma. *Eur Radiol* 2018;28:2184-2193
28. Kobayashi S, Nakanuma Y, Matsui O. Intrahepatic peribiliary vascular plexus in various hepatobiliary diseases: a histological survey. *Hum Pathol* 1994;25:940-946