고빌리루빈혈증과 담도 침범을 동반한 간세포암에 대한 경동맥화학 리피오돌색전술의 안전성과 예후 인자

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Transarterial Chemolipiodolization for Hepatocellular Carcinoma with Central Bile Duct Invasion Causing Conjugated Hyperbilirubinemia: Safety and Prognostic Factors for Survival

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Background/Aims: The treatments and outcomes of hepatocellular carcinoma (HCC) with bile duct invasion are not well known. We aimed to confirm the safety of transarterial chemolipiodolization (TACL) and identify prognostic factors for patients with bile duct invasion treated with TACL.

Methods: Fifty patients with central bile duct invasion treated with TACL between 2005 and 2017 were enrolled. Patients were divided into three groups: hyperbilirubinemia (total bilirubin ≥ 2.5 mg/dL) with pre-TACL biliary drainage, hyperbilirubinemia without biliary drainage, and without hyperbilirubinemia. Tumor response to TACL, survival outcomes, length of hospitalization, adverse events using Common Terminology Criteria for Adverse Events (CTCAE), and factors affecting overall survival were compared.

Results: TACL-induced changes of mean CTCAE grades for albumin, alanine aminotransferase, creatinine, prothrombin time, and platelet were not significantly different among patients with or without initial hyperbilirubinemia. Serum bilirubin level was not significantly changed after TACL in all the three groups. Overall survival was not significantly different among the three groups ($P=0.097$). On multivariate analysis, alpha-fetoprotein <400 ng/dL (hazard ratio [HR]=0.477, $P=0.048$) and highest total bilirubin level of <2.5 mg/dL within one month after TACL (HR=0.335, $P=0.004$) were significantly associated with longer survival.

Conclusions: TACL was a safe treatment for HCC patients with central bile duct invasion, irrespective of the presence of initial hyperbilirubinemia. (J Liver Cancer 2018;18:121-129)

Keywords: Hepatocellular carcinoma; Chemoembolization, Therapeutic; Bile duct; Hyperbilirubinemia

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and the third leading cause of cancer-related mortality worldwide.¹ HCC with jaundice as the primary clinical manifestation is uncommon; approximately 1-12% of patients have jaundice at the first diagnosis.² Conjugated hyperbilirubinemia of HCC is generally caused by a deterioration of the liver function due to the progression of underlying liver cirrhosis or extensive infiltration of the liver parenchyma by HCC.³ For these patients, aggressive treatments may exacerbate the liver function decline, and palliative treatments are recommended.⁴

Bile duct invasion in HCC is found with a low incidence (0.5-13%) and may present with obstructive jaundice as the initial clinical manifestation.² This icteric type of HCC can cause recognizable jaundice even if the tumor size is small, unlike other types of HCC.⁵ Although bile duct invasion in HCC is relatively uncommon, the diagnosis should require differentiation from other biliary tract diseases that can cause obstructive jaundice and may accompany complications such as cholangitis and hemobilia.⁴ According to previous reports, patients with bile duct invasion have a poor prognosis because of the high rates of vascular invasion or portal vein tumor thrombus (PVTT).^{6,7} However, some researchers

have suggested that early detection due to obstructive jaundice can lead to opportunities for treatment.⁴ A standard treatment for HCC patients with bile duct invasion has not been established due to limited data, and the prognosis of such patients has not been studied in detail previously.

In HCC patients presenting with obstructive jaundice, hyperbilirubinemia itself is difficult to use to access hepatic functional reserve. However, hyperbilirubinemia has been considered as a relative contraindication to transarterial chemolipiodolization (TACL) in the current clinical guidelines;⁸ therefore, endoscopic or percutaneous biliary drainages are often performed before TACL.⁹ For patients with conjugated hyperbilirubinemia caused by unresectable HCC with central bile duct invasion, it has been reported that effective biliary drainage followed by TACL may prolong survival.^{6,10} Few reports have compared the clinical outcomes between tumors with central bile duct invasion causing conjugated hyperbilirubinemia and tumors with central bile duct invasion without hyperbilirubinemia after TACL.¹¹

In this study, we evaluated the clinical characteristics and safety of TACL for HCC patients with central bile duct invasion. Furthermore, through the analyses of the safety of TACL and survival outcomes in subgroups, we also aimed to evaluate the necessity of biliary drainage before TACL and the feasibility of TACL in patients with obstructive jaundice.

Figure 1. Patient demographics. HCC, hepatocellular carcinoma; TACL, transarterial chemolipiodolization.

METHODS

1. Study design and population

This study was conducted after approval from the Institutional Review Board of Seoul St. Mary's Hospital (KC18RE-SI0399). We retrospectively reviewed the medical records of all patients diagnosed with HCC at our institution between January 2006 and December 2016. A total of 1,154 patients were identified, and 50 patients with central bile duct invasion by HCC treated with TACL were enrolled (Fig. 1). Central bile duct invasion was defined as an invasion by the tumor of the right hepatic duct, the left hepatic duct, or the common hepatic duct. Among the 50 patients enrolled in the analysis, 24 had obstructive jaundice (total bilirubin ≥ 2.5 mg/dL) at initial diagnosis, and 26 did not have obstructive jaundice (total bilirubin < 2.5 mg/dL). Of the 24 patients with obstructive jaundice, 12 underwent biliary drainage before TACL, and 12 underwent TACL without biliary drainage (Fig. 1). All patients included in this study were followed up until March 2018, and survival of patients was confirmed by the National Health Insurance Service.

2. Diagnosis of HCC

The diagnosis of HCC was based on the latest guidelines from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases.^{12,13} Dynamic imaging modalities, including multiphasic computed tomography (CT) and magnetic resonance imaging (MRI), and tumor markers, such as alpha-fetoprotein (AFP), were used for the diagnosis of HCC. Liver biopsy was performed for pathological confirmation if HCC and other malignancies could not be distinguished by radiological findings. Bile duct tumor invasion was diagnosed when direct intraductal invasion by HCC of the liver parenchyma was identified in imaging studies.^{11,14}

3. Procedures

When obstructive jaundice was identified at the first diag-

nosis of HCC, the decision to perform biliary drainage was by hepatologists. Obstructive jaundice was defined as hyperbilirubinemia (≥ 2.5 mg/dL) caused by the obstruction of central bile ducts.³ The biliary drainages were determined according to clinician's preference, bile duct dilation and the feasibility in imaging studies for biliary drainage. Percutaneous transhepatic biliary drainage (PTBD) was performed by interventional radiologists when the endoscopic approach failed, or the percutaneous approach was favorable for the obstructive lesion. The specific process of PTBD used in our institution has been described in a previous report.¹⁵ If evidence of inflammation such as acute cholangitis was present, patients were given antibiotics before and after the procedures until the infection improved.

The detailed TACL procedure has been reported previously.¹⁶ Patients who underwent TACL were treated with intra-arterial doxorubicin (40-60 mg) or a combination of epirubicin (40-60 mg) and cisplatin (60-70 mg) with a mixture of lipiodol (5-10 mL).¹⁷ The intensity of locoregional treatment was determined by tumor stage, liver function, or the presence of PVTT.¹⁸ In patients with hyperbilirubinemia, clinicians carefully performed TACL according to the assessment of the hepatic functional reserve. Tumor response was assessed based on modified Response Evaluation Criteria in Solid Tumors (mRECIST) using multiphasic CT or MRI after one or two months of TACL. TACL was repeated every four to eight weeks when patients had no deterioration of liver function and viable tumor lesions were present in follow-up imaging studies.

4. Statistical analyses

For the baseline clinical characteristics, continuous variables were expressed as the mean value and range with standard deviation. The independent *t*-test was used to compare continuous variables between the two groups. Categorical variables were presented as number and percentage of the subjects. The chi-square test and Fisher's exact test were used to compare categorical variables. Overall survival, the primary endpoint in this study, was estimated by the Kaplan-Meier method and compared using the log-rank test. To evaluate

the factors affecting overall survival, multivariate analysis using a Cox proportional hazards model was performed. All data were considered statistically significant when the *P*-value was <0.05 . The Statistical Package for the Social Sciences (SPSS version 24.0, IBM corp., Armonk, NY, USA) was used for all statistical analyses.

Table 1. Baseline clinical characteristics

Variable	Patients with bilirubin ≥ 2.5 (n=24)	Patients with bilirubin < 2.5 (n=26)	P-value
Sex			
Male	17 (70.8)	22 (84.6)	0.162
Female	7 (29.2)	4 (15.4)	
Age			
<55	12 (50.0)	17 (65.4)	0.208
≥ 55	12 (50.0)	9 (34.6)	
Etiology			
HBV	18 (75)	19 (73)	0.031
HCV	0 (0)	5 (19)	
Others	6 (25)	2 (8)	
AFP at diagnosis			
<400 ng/mL	14 (58.3)	10 (38.5)	0.257
≥ 400 ng/mL	10 (41.7)	16 (61.5)	
Mean albumin	3.19 ± 0.48	3.49 ± 0.52	0.674
Child-Pugh class			
A	8 (33.3)	22 (84.6)	<0.001
B/C	16 (66.7)	4 (15.4)	
Tumor size			
<5 cm	6 (25)	7 (27)	1
≥ 5 cm	18 (75)	19 (73)	
Multiple tumors			
Yes	12 (50)	15 (58)	0.777
No	12 (50)	11 (42)	
Portal vein tumor thrombosis			
Yes	15 (62.5)	14 (53.8)	0.578
No	9 (37.5)	12 (46.2)	
Extrahepatic metastasis			
Yes	5 (20.8)	5 (19.2)	1
No	19 (79.2)	21 (80.8)	
Previous TACL			
Yes	8 (33.3)	6 (23.1)	0.533
No	16 (66.7)	20 (76.9)	

Values are presented as mean $\pm$ standard deviation or number (%). HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein; SD, standard deviation; TACL, transarterial chemolipiodolization.

RESULTS

1. Baseline clinical characteristics

Table 1 shows the baseline clinical characteristics of the HCC patients with central bile duct invasion treated with TACL. Patients with central bile duct invasion (n=50) were divided into those with obstructive jaundice (total bilirubin ≥ 2.5 mg/dL, n=24) and those without obstructive jaundice (total bilirubin < 2.5 mg/dL, n=26). Of the 50 patients, 39 (78%) were male, and 29 (58%) were older than 55 years. The major cause of the underlying liver disease was hepatitis B virus infection in both. There were no significant differences regarding sex, age, AFP at diagnosis, mean albumin level, tumor size, the number of tumors, the presence of PVTT, extrahepatic metastasis at diagnosis, and previous history of TACL between the two groups. In the group with obstructive jaundice, more patients had advanced Child-Pugh class (class B or C, 66.7% vs. 15.4%; $P<0.001$) than those without obstructive jaundice due to elevated bilirubin levels (Table 1).

2. Tumor response at the first response evaluation of TACL

In all patients who underwent TACL, tumor response was evaluated using follow-up CT or MRI after one or two months based on mRECIST (Table 2). Complete response (CR) was defined as the disappearance of tumoral arterial enhancement of all target lesions; partial response (PR) was

Table 2. Tumor response at the first response evaluation of TACL

	Patients with bilirubin ≥ 2.5 (n=24)	Patients with bilirubin < 2.5 (n=26)	P-value*
Complete response	0	2	0.573
Partial response	10	9	0.573
Stable disease	6	9	0.573
Progressive disease	7	5	0.573
No follow-up	1	1	0.573

TACL, transarterial chemolipiodolization.

*The chi-square test and Fisher's exact test were used.

defined as a decrease in the sum of the diameters of viable target lesions by more than 30%; progressive disease (PD) was defined as an increase in the sum of viable target lesions by more than 20%; and stable disease (SD) was defined as any cases that did not qualify for PR or PD.¹⁹ In the patients with obstructive jaundice, none achieved CR. Ten, six, and seven patients presented PR, SD, and PD, respectively. In the patients without obstructive jaundice, two achieved CR and nine achieved PR. Five patients presented PD and nine presented SD (Table 2). As a result, there was no significant difference in tumor response between the two groups ($P=0.573$).

3. Safety of TACL for HCC with central bile duct invasion

The mean length of hospital stay for patients who underwent TACL at our institution is 6.2 days, irrespective of the presence of bile duct invasion. The mean period of hospitalization is shorter for patients without hyperbilirubinemia than for those with hyperbilirubinemia (10.2 vs. 14.5 days, $P=0.017$; Fig. 2A). Patients with hyperbilirubinemia were subdivided into two groups according to the presence of biliary drainage to precisely evaluate the safety of TACL. The mean length of hospital stay for patients with biliary drainage was shorter than for those without biliary drainage (12.7 vs.

16.3 days; Fig. 2A).

To analyze the adverse effects associated with TACL, we used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The laboratory parameters for the adverse effects of TACL were total bilirubin, albumin, alanine aminotransferase, creatinine, prothrombin time, and platelet reflecting the change in hepatic functional reserve after the procedures (Fig. 2B). Among the parameters, only total bilirubin level was significantly decreased in the patients with biliary drainage before TACL (mean of differences, 5.860; $P=0.002$). Changes in CTCAE grades for the other factors were not significantly different among all groups (Fig. 2B).

In addition, we compared the changes in total bilirubin level between that on the day of TACL and the highest level within one month after TACL in each group (Fig. 3). Similar to the results in Fig. 2B, post-drainage total bilirubin level was significantly decreased in the patients who underwent pre-TACL biliary drainage. However, there was no significant difference in total bilirubin after TACL in all three groups ($P=0.106$, $P=0.20$, and $P=0.16$, respectively).

Figure 2. Safety of TACL for HCC with central bile duct invasion. (A) Length of hospital stay (days). (B) Changes in CTCAE grade (albumin, bilirubin, alanine aminotransferase, creatinine, INR, platelet). TACL, transarterial chemolipiodolization; HCC, hepatocellular carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; INR, international normalized ratio; ALT, alanine aminotransferase; PT, prothrombin time.

4. Survival outcomes in patients with central bile duct invasion according to the treatments

Next, we analyzed the survival outcomes in each subgroup using the Kaplan-Meier method (Fig. 4). Fig. 4A shows the overall survival rate of patients with or without hyperbiliru-

binemia. In the group with hyperbilirubinemia, the median survival period was 6.6 months, and the one-year survival rate was 22.7%. In the group without hyperbilirubinemia, the median survival period was 4.8 months, and the one-year survival rate was 18.2%. There was no significant difference in the overall survival rates between the two groups ($P=0.097$).

Figure 3. Safety of TACL for HCC with central bile duct invasion: change in total bilirubin. TACL, transarterial chemolipiodolization; HCC, hepatocellular carcinoma.

Figure 4. Kaplan-Meier estimates of overall survival according to the treatments. (A) Overall survival rate of patients with or without hyperbilirubinemia. (B) Overall survival rate between patients with pre-TACL biliary drainage, patients without pre-TACL biliary drainage, and patients without hyperbilirubinemia. TACL, transarterial chemolipiodolization.

When patients with hyperbilirubinemia were subdivided according to pre-TACL biliary drainage, the median survival period and the one-year survival rate of patients who underwent pre-TACL biliary drainage were 7.0 months and 35.4% (Fig. 4B). In patients without pre-TACL biliary drainage, the median survival period and the one-year survival rate were 4.8 months and 25%. In this case, however, there were no statistically significant differences among the three groups ($P=0.170$).

5. Multivariate analyses for overall survival in patients with central bile duct invasion

Subsequently, univariate and multivariate analyses using a Cox proportional hazards model were performed to investigate the factors affecting overall survival (Table 3). As shown in Table 3, the significant factors influencing the survival outcomes of HCC patients with central bile duct invasion were as follows: highest total bilirubin <2.5 mg/dL within one month after TACL ($P=0.005$), multiple tumors ($P=0.003$), AFP <400 ng/dL ($P=0.008$), and favorable tumor response (CR or PR, $P=0.005$). On multivariate analysis, AFP <400 ng/dL (hazard ratio [HR]=0.477, 95% confidence interval [CI] 0.229-0.995, $P=0.048$) and highest total bilirubin <2.5 mg/dL within one month after TACL (HR=0.335, 95% CI

0.158-0.710, $P=0.004$) were the factors associated with a significantly longer survival.

DISCUSSION

A standard treatment strategy for HCC patients with central bile duct invasion has not been established because of the lack of detailed evidence.³ In addition, the characteristics and prognosis of HCC in such patients are not well known. According to the results of previous studies reported to date, HCC patients with bile duct invasion showed a worse prognosis than patients without bile duct invasion.^{7,20} Thus far, TACL is the only treatment modality for controlling intrahepatic tumor lesions in patients with bile duct invasion; however, the efficacy and safety of the treatment are still controversial.¹¹ Radiofrequency ablation can cause life-threatening complications such as structural injuries in bile ducts or intrahepatic vessels, and transarterial radioembolization or radiation therapy as an alternative to TACL are not commonly used methods for these patients. In this study, we found that TACL was safe for patients with central bile duct invasion, and initial conjugated hyperbilirubinemia did not affect prognosis or survival.

In previous studies about the icteric type of HCC, patients with bile duct invasion were most likely to have a poor prog-

Table 3. Univariate and multivariate analyses for overall survival

Variable	Univariate analysis (Kaplan-Meier and log-rank test)		Multivariate analysis (Cox proportional hazards model)	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age ($<55/\geq 55$)	0.295	0.705 (0.367-1.355)		
Sex (female / male)	0.146	0.353 (0.106-1.173)		
Child-Pugh Class (A/B or C)	0.903	0.961 (0.505-1.828)		
Total bilirubin before TACL ($<2.5/\geq 2.5$)	0.888	0.956 (0.510-1.792)		
Total bilirubin after TACL ($<2.5/\geq 2.5$)	0.005	0.374 (0.188-0.744)	0.004	0.335 (0.158-0.710)
Size (<5 cm/ ≥ 5 cm)	0.749	0.889 (0.432-1.828)		
Multiple tumors (no/yes)	0.003	0.334 (0.163-0.682)	0.141	0.541 (0.206-1.225)
PVTT (no/yes)	0.577	0.836 (0.446-1.570)		
AFP ($<400/\geq 400$)	0.008	0.415 (0.217-0.792)	0.048	0.477 (0.229-0.995)
Presence of extrahepatic spread (no/yes)	0.447	0.745 (0.348-1.593)		
TACL response (CR+PR/SD+PD)	0.005	0.352 (0.170-0.730)	0.1	0.518 (0.236-1.134)

HR, hazard ratio; CI, confidence interval; TACL, transarterial chemolipiodolization; PVTT, portal vein tumor thrombus; AFP, alpha fetoprotein; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

nosis because of the strong association with vascular invasion and PVTT.⁷ In those studies, PVTT was present in up to 88% of cases with bile duct invasion. In our results, PVTT was found in 62% of patients with hyperbilirubinemia and 54% of patients without hyperbilirubinemia; however, PVTT was not a significant factor affecting overall survival in the univariate analysis (Table 3). This is probably because other studies included relatively more patients with advanced hepatic dysfunction compared to our study.

Endoscopic biliary drainage or PTBD is performed for the decompression of a biliary tract if patients presented obstructive jaundice as a clinical manifestation or had bile duct dilatation in imaging studies at the initial diagnosis. According to some researchers, effective biliary drainage improves survival outcomes in patients with bile duct invasion.^{6,10} However, according to the results of our study, the presence of biliary drainage (endoscopic or percutaneous) had no significant effect on the survival of patients. It is difficult to accurately evaluate liver function in patients with hyperbilirubinemia caused by biliary obstruction by a tumor rather than by deteriorated function of liver parenchyma. According to a prospective study conducted by Lau et al.²¹, patients with obstructive jaundice secondary to tumor had similar survival outcomes to those without jaundice. Our results are in agreement with their findings, and consequently, patients' prognoses were found to be related to the extent of disease progression and the location and size of the tumor within the bile duct.

We analyzed changes in CTCAE grade to clarify the safety of TACL in patients with central bile duct invasion. Our results indicated that hyperbilirubinemia or pre-TACL drainage did not affect changes in CTCAE factors reflecting liver function. There was also no significant difference in hospital stays for each subgroup. Univariate and multivariate analyses confirmed that survival outcomes were dependent on the highest bilirubin level within one month after TACL rather than on initial hyperbilirubinemia or pre-TACL biliary drainage. These results support that TACL can be performed relatively safely even in cases with central bile duct invasion. We emphasize that hyperbilirubinemia in patients with central bile duct invasion does not reflect intact liver function.

In other words, Child-Pugh classification and the Barcelona Clinic Liver Cancer staging system for HCC may be overestimated in these patients.

Our study has some limitations. First, patients' medical information was obtained retrospectively, and the study was conducted in a single institution. Second, because the study was performed in a hepatitis B virus-endemic area, the proportion of tumor characteristics caused by other factors such as hepatitis C virus infection or alcohol is unclear. Third, the number of enrolled patients was relatively small making it difficult to confirm characteristic differences in each group.

In conclusion, TACL is a safe treatment modality for HCC patients with central bile duct invasion. A highest total bilirubin level of <2.5 mg/dL within one month after TACL was more important for favorable prognosis than initial hyperbilirubinemia or biliary drainage before TACL. Because of the lack of evidence from large-scale and prospective studies in such patients, additional research should be undertaken in the future.

ETHICS APPROVAL

Ethics approval was provided by the Ethics Review Board of the Catholic University of Korea (KC18RESI0399).

AUTHOR CONTRIBUTIONS

Keungmo Yang, Pil Soo Sung, Seung Kew Yoon: study design, data collection, data analysis, data interpretation, and manuscript writing and approval. Jeong Won Jang, Si Hyun Bae, and Jong Young Choi: data analysis, data interpretation, and manuscript approval. Jung Suk Oh and Ho Jong Chun: data interpretation and manuscript approval.

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Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2016;2:16018.
2. Huang JF, Wang LY, Lin ZY, Chen SC, Hsieh MY, Chuang WL, et al. Incidence and clinical outcome of icteric type hepatocellular carcinoma. *J Gastroenterol Hepatol* 2002;17:190-195.
3. Lai EC, Lau WY. Hepatocellular carcinoma presenting with obstructive jaundice. *ANZ J Surg* 2006;76:631-636.
4. Qin LX, Tang ZY. Hepatocellular carcinoma with obstructive jaundice: diagnosis, treatment and prognosis. *World J Gastroenterol* 2003;9:385-391.
5. Lau WY, Leow CK, Leung KL, Leung TW, Chan M, Yu SC. Cholangiographic features in the diagnosis and management of obstructive icteric type hepatocellular carcinoma. *HPB Surg* 2000;11:299-306.
6. Suh YG, Kim DY, Han KH, Seong J. Effective biliary drainage and proper treatment improve outcomes of hepatocellular carcinoma with obstructive jaundice. *Gut Liver* 2014;8:526-535.
7. An J, Lee KS, Kim KM, Park DH, Lee SS, Lee D, et al. Clinical features and outcomes of patients with hepatocellular carcinoma complicated with bile duct invasion. *Clin mol Hepatol* 2017;23:160-169.
8. Han K, Kim JH. Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system. *World J Gastroenterol* 2015;21:10327-10335.
9. Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13(9 Pt 2):S211-S221.
10. Choi J, Ryu JK, Lee SH, Hwang JH, Ahn DW, Kim YT, et al. Palliative treatment of unresectable hepatocellular carcinoma with obstructive jaundice using biliary drainage with subsequent transarterial chemoembolization. *J Palliat Med* 2013;16:1026-1033.
11. Choi JW, Chung JW, Cho YK, Kim YJ, Yoon JH, Kim HC, et al. Transarterial chemoembolization for hepatocellular carcinomas with central bile duct invasion: safety, prognosis, and predictive factors. *Cardiovasc Intervent Radiol* 2015;38:937-945.
12. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908-943.
13. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358-380.
14. Jung AY, Lee JM, Choi SH, Kim SH, Lee JY, Kim SW, et al. CT features of an intraductal polypoid mass: differentiation between hepatocellular carcinoma with bile duct tumor invasion and intraductal papillary cholangiocarcinoma. *J Comput Assist Tomogr* 2006;30:173-181.
15. Chang JH, Lee IS, Choi JY, Yoon SK, Kim DG, You YK, et al. Biliary stricture after adult right-lobe living-donor liver transplantation with duct-to-duct anastomosis: long-term outcome and its related factors after endoscopic treatment. *Gut Liver* 2010;4:226-233.
16. Jang JW, Kim YW, Lee SW, Kwon JH, Nam SW, Bae SH, et al. Reactivation of hepatitis B virus in HBsAg-negative patients with hepatocellular carcinoma. *PLoS One* 2015;10:e0122041.
17. 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.
18. Jang JW, Kwon JH, You CR, Kim JD, Woo HY, Bae SH, et al. Risk of HBV reactivation according to viral status and treatment intensity in patients with hepatocellular carcinoma. *Antivir Ther* 2011;16:969-977.
19. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
20. Yeh CN, Jan YY, Lee WC, Chen MF. Hepatic resection for hepatocellular carcinoma with obstructive jaundice due to biliary tumor thrombi. *World J Surg* 2004;28:471-475.
21. Lau W, Leung K, Leung TW, Liew CT, Chan MS, Yu SC, et al. A logical approach to hepatocellular carcinoma presenting with jaundice. *Ann Surg* 1997;225:281-285.