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Research Paper

Transcatheter Arterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma: Clinical Outcome and Safety in Elderly Patients

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Abstract

Aim: The aim of our study was to compare clinical outcomes between elderly patients aged ≥75 years (elderly group, n=66) with intermediate hepatocellular carcinoma (HCC) undergoing transcatheter arterial chemoembolization (TACE) and younger patients aged <75 years (control group, n=84) with intermediate HCC undergoing TACE.

Methods: Clinical outcomes, including overall survival (OS) and tumor response rate at initial therapy, were compared between these two groups.

Results: The median survival time and the 1- and 3-year cumulative OS rates were 2.90 years and 84.1% and 48.0%, respectively, in the elderly group and 2.44 years and 78.2% and 39.3%, respectively, in the control group (p=0.887). The objective response rate in the elderly group was 81.8% (54/66 patients), while that in the control group was 78.6% (66/84 patients) (p=0.227).

Conclusion: Elderly patients with intermediate HCC undergoing TACE had a prognosis comparable with that of younger patients with intermediate HCC undergoing TACE.

Key words: transcatheter arterial chemoembolization, intermediate hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is a major health problem. It is the fifth most common type of cancer worldwide and the third most common cause of cancer-related death (1-3). The prognosis for untreated HCC is poor in general, and the curative treatments for this disease comprise surgical resection, radiofrequency ablation, and liver transplantation (1-3). Noncurative therapies for HCC include transcatheter arterial chemoembolization (TACE), radioembolization, molecular targeting therapies such as sorafenib, and radiation therapy (1-8).

Societal aging implies that the number of elderly patients with malignancy will rise in the future (9). In Japan, 75-year-old men and women have an average expected life span of around 5 and 10 years, respectively, and Japan has the greatest longevity in the world (10). The risk of developing HCC is known to be age-dependent, and patients aged ≥75 years sometimes present with HCC (11, 12). The increased longevity of the population means that more elderly patients with HCC are to be expected in the coming years. In Japan, the adjusted HCC mortality has increased in recent years (13). Moreover, the average age of patients with HCC in Japan is increasing, as is the proportion of elderly patients with HCC (14). Thus, there is an urgent need to identify the optimal

management for HCC in elderly patients.

TACE is a procedure whereby an embolic agent is injected into the tumor-feeding artery to deprive the tumor of its major nutrient source by means of embolization; this results in ischemic necrosis of the targeted tumor (8). The survival benefit of TACE in patients with unresectable HCC was established in two randomized controlled trials and one meta-analysis (15-17). Thus, TACE plays an important role in the treatment of unresectable HCC. It is clearly defined as a first-line therapy with a better 2-year survival rate than that of conservative therapy (18). The Barcelona Clinic Liver Cancer (BCLC) intermediate stage (BCLC-B) includes Child-Pugh A and B patients with multifocal HCC, defined as more than three tumors of any size or two to three tumors with a maximal diameter of ≤3 cm and a single HCC of ≤5 cm (18-21). The BCLC classification indicates that these patients are optimal candidates for TACE (18, 19).

Advanced age was previously considered to be a contraindication for TACE in the treatment of HCC (22). There are few data regarding the clinical outcome in elderly patients with intermediate HCC undergoing TACE (21, 23-26) and most of them are reported from countries other than Japan. Furthermore, the BCLC classification does not stratify strategies according to age (18, 19). Whether elderly patients with intermediate HCC who undergo TACE have a prognosis comparable with that of younger patients with intermediate HCC who undergo TACE therefore remains elusive (21, 23-25). The aim of the present study was to compare clinical outcomes between elderly patients with intermediate HCC undergoing TACE and younger patients with intermediate HCC undergoing TACE.

Materials and Methods

Patients. We performed TACE as an initial treatment in 150 treatment-naive patients diagnosed with intermediate-stage HCC in the Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan between December 2003 and December 2012. Of these patients, 147 were treated with TACE using an epirubicin-mitomycin-lipiodol (EML) emulsion, and three were treated with TACE using a miriplatin-lipiodol emulsion. We categorized them into two groups: the elderly group (≥75 years old, n=66) and the control group (<75 years old, n=84). The breakpoint of 75 years of age was chosen because in Japan, patients aged ≥75 years are covered by a health insurance system that differs from that for patients aged <75 years. We compared the clinical outcomes including overall survival (OS), tumor response rate, and safety between these two groups. Patients diagnosed with HCC rupture at initial therapy were not included in this study because they were treated with transcatheter arterial embolization without chemoembolization.

Written informed consent was obtained from all patients prior to each therapy, and the study protocol complied with all provisions of the Declaration of Helsinki. This study was approved by the Ethics Committee of Osaka Red Cross Hospital, Japan, and the need for written informed consent was waived because the data were analyzed retrospectively and anonymously. The present study comprised a retrospective analysis of patient records registered in our database, and all treatments were conducted in an open-label manner.

HCC diagnosis. HCC was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase) and/or magnetic resonance imaging (MRI), based mainly on the recommendations of the American Association for the Study of Liver Diseases (18). Arterial- and portal-phase dynamic CT images were obtained at approximately 30 and 120 s, respectively, after the injection of the contrast material. When carrying out angiography, we also confirmed the presence of intermediate-stage HCC using CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP) (27, 28).

TACE procedure. In our angiography room, a catheter was advanced to the superior mesenteric artery, and CTAP was performed to investigate the site and size of the HCC. Furthermore, we confirmed the patency of the portal vein at the time of postmesenteric portography. A catheter was then advanced to the celiac artery, and a microcatheter was advanced to the common hepatic artery or proper hepatic artery through a catheter. This approach was used to perform CTHA and digital subtraction angiography with the purpose of investigating the tumor vascularity and identifying the feeding vessels. After the completion of these procedures, a microcatheter was advanced as close as possible to the feeding vessels of the targeted tumor. This was followed by intra-arterial infusion of an anticancer agent and lipiodol emulsion via the feeding arteries according to tumor size and liver function (20, 29, 30). After the infusion of the anticancer agent and lipiodol emulsion, gelatin sponge particles were slowly injected into the feeding arteries to prevent reflux into untreated segments. The sites of injection of the embolizing agents were segmental or subsegmental in all patients treated with TACE. When patients had poor liver function, the doses of the anticancer agents and lipiodol were reduced.

Assessment of treatment efficacy. Treatment efficacy was evaluated using CT findings within 2 months after the initial treatment. We regarded lipiodol accumulation in targeted tumors seen on CT scans as an indication of necrosis. This was because several studies previously reported that the lipiodol retention areas observed on CT corresponded to necrotic areas (31, 32). A complete response (CR) was defined as the disappearance of all targeted tumors or 100% tumor necrosis, a partial response (PR) was defined as a ≥50% reduction in tumor size and/or necrosis, and progressive disease (PD) was defined as >25% tumor enlargement and/or the appearance of any new HCC tumors. Stable disease (SD) was defined as disease that did not qualify for classification as CR, PR, or PD.

Follow-up. Follow-up after each therapy comprised periodic blood tests and monitoring of tumor markers, including α-fetoprotein and *des*-γ-carboxy prothrombin. Dynamic CT scans and/or MRI were obtained every 2 to 4 months after each therapy. Chest CT, whole abdominal CT, brain MRI, and bone scintigraphy were performed when extrahepatic HCC recurrence was suspected. When disease progression of the treated HCC lesions was observed after the initial therapy and/or new hepatic lesions were observed, the most appropriate treatments were performed if the liver functional reserve was adequate and if patients did not refuse such therapies. These treatments included transcatheter arterial therapies in most cases. However, when the treated lesion was well controlled after the initial therapy and the new lesion appeared in the liver, percutaneous ablative therapies were also considered. In cases that were refractory to transcatheter arterial therapies or those involving extrahepatic metastases, a molecular targeting therapy such as sorafenib was also considered (33).

Statistical analysis. Data were analyzed using univariate and multivariate analyses. Continuous variables were compared using the unpaired *t*-test, and categorical variables were compared using Fisher's exact test. For analysis of OS, follow-up ended at the time of death from any cause, and the remaining patients were censored at the last follow-up visit. The cumulative OS rates were calculated using the Kaplan-Meier method and tested using the log-rank test. Factors with a p value of <0.05 in univariate analysis were subjected to multivariate analysis using the Cox proportional hazards model. These statistical methods were used to estimate the interval from initial treatment. Data were analyzed using SPSS software (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Data are expressed as the mean ± standard deviation. Values of $p<0.05$ were considered to be statistically significant.

Results

Baseline characteristics. The baseline characteristics of the patients in the two groups are shown in Table I. The median observation periods were 1.6 years (range, 0.2–5.3 years) in the elderly group and 1.9 years (range, 0.2–9.0 years) in the control group. There was a significantly higher proportion of female patients, a lower positivity rate for hepatitis B surface antigen, and a lower body mass index (BMI) in the elderly group. The serum albumin level, prothrombin time (PT), and platelet count were significantly higher in the elderly group than in the control group, and the proportion of patients with Child-Pugh class A disease was significantly higher in the elderly group than in the control group. These findings indicated that patients in the elderly group had a liver functional reserve superior to that of patients in the control group. No significant difference was observed in comorbid diseases between the two groups.

Table I. Baseline characteristics between the elderly group and the control group.

Variables	Elderly group (n=66)	Control group (n=84)	P value
Age (years)	80.8 ± 4.2	65.7 ± 5.6	< 0.001[a]
Gender, male/female	34 / 32	63 / 21	0.003[b]
Maximum tumor size (cm)	5.7 ± 2.8	5.1 ± 3.2	0.220[a]
Tumor distribution, bilobar/unilobar	23 / 43	37 / 47	0.314[b]
Tumor number, >5 vs. ≤5	14 / 52	21 / 63	0.698[b]
Child-Pugh classification			
Child-Pugh A / B	53 / 13	52 / 32	0.019[b]
Causes of liver disease			
B/C/non B and non C/B and C	0 / 47 / 19 / 0	13 / 49 / 21 / 1	0.003[b]
Efficacy of initial TACE			
CR/PR/SD/PD	10/44/11/1	20/46/18/0	0.227[b]
AST (IU/L)	58.2 ± 29.6	63.8 ± 34.0	0.289[a]
ALT (IU/L)	43.5 ± 27.9	52.9 ± 37.7	0.095[a]
ALP (IU/L)	383.6 ± 193.4	439.1 ± 235.8	0.124[a]
GGT (IU/L)	119.0 ± 182.6	157.3 ± 211.1	0.244[a]
Serum albumin (g/dL)	3.78 ± 0.48	3.53 ± 0.52	0.003[a]
Total bilirubin (mg/dL)	0.95 ± 0.64	1.15 ± 0.96	0.151[a]
Prothrombin time (%)	88.4 ± 18.4	81.0 ± 17.0	0.012[a]
Platelets ($\times 10^4/mm^3$)	15.6 ± 7.7	12.4 ± 6.5	0.007[a]
AFP (ng/mL)	1367.6 ± 3614.3	1250.8 ± 3679.8	0.846[a]
DCP (mAU/mL)	7046.4 ± 19775.1	10076.1 ± 42352.1	0.563[a]
Duration of hospitalization (days)	10.7 ± 5.0	12.6 ± 6.7	0.053[a]
Body mass index (kg/m^2)	21.8 ± 3.7	24.6 ± 3.6	<0.001[a]
Comorbid diseases			
Hypertension, yes/no	44 / 22	43 / 41	0.068[b]
Cardiovascular disease, yes/no	14 / 52	12 / 72	0.285[b]
Respiratory disease, yes/no	4 / 62	7 / 77	0.756[b]
Cerebrovascular disease, yes/no	11 / 55	13 / 71	>0.999[b]
Diabetes mellitus, yes/no	19 / 47	35 / 49	0.124[b]
Serum creatinine (mg/dL)	0.98 ± 0.49	0.90 ± 0.37	0.270[a]

Data are expressed as number or mean ± standard deviation. TACE; transcatheter arterial chemoembolization, CR; complete response, PR; partial response, SD; stable disease, PD; progressive disease, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, [a]; unpaired t test, [b]; Fisher's exact test.

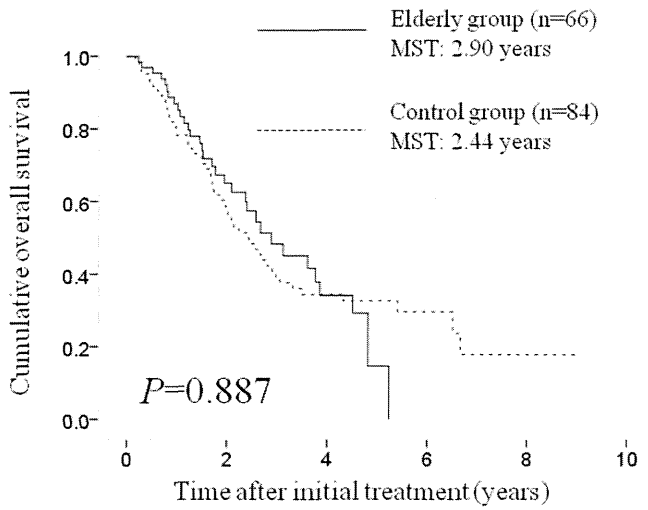

Figure 1. Median survival time (MST) and cumulative overall survival (OS). The MST and the 1-, 3-, and 5-year cumulative OS rates were 2.90 years and 84.1%, 48.0%, and 15.0%, respectively, in the elderly group and 2.44 years and 78.2%, 39.3%, and 33.8%, respectively, in the control group (p=0.887). MST: median survival time.

Median survival time and cumulative OS rates. The median survival time (MST) and the 1-, 3-, and 5-year cumulative OS rates were 2.90 years and 84.1%, 48.0%, and 15.0%, respectively, in the elderly group and 2.44 years and 78.2%, 39.3%, and 33.8%, respectively, in the control group; there was no significant difference between the two groups (p=0.887) (Figure 1).

Mean doses of anticancer agents and lipiodol in the two groups. In the elderly group, TACE using EML emulsion containing epirubicin (Farmorubicin; Pfizer) at a mean dose of 39.1 ± 9.8 mg, mitomycin (Mitomycin C; Kyowa Hakko Kirin Company, Ltd., Tokyo, Japan) at a mean dose of 8.8 ± 3.3 mg, and lipiodol at a mean dose of 5.9 ± 2.8 ml was performed in 65 patients, and TACE using miriplatin-lipiodol emulsion containing miriplatin (Miripla; Dainippon Sumitomo, Tokyo, Japan) at a dose of 140 mg and lipiodol at a dose of 7 ml was performed in 1 patient (29, 30, 34). In the control group, TACE using EML emulsion containing epirubicin at a mean dose of 39.3 ± 10.9 mg, mitomycin at a mean dose of 8.9 ± 3.1 mg, and lipiodol at a mean dose of 5.6 ± 2.7 ml was performed in 82 patients, and TACE using miriplatin-lipiodol emulsion containing miriplatin at a dose of 120 mg and lipiodol at a dose of 6 ml was performed in 2 patients (29, 30, 34).

Treatment efficacy at initial treatment in the two groups. In the elderly group, a CR was achieved in 10 patients, a PR in 44 patients, SD in 11 patients, and PD in 1 patient. Thus, the objective response rate (ORR) in the elderly group was 81.8% (54/66 patients). In the control group, a CR was achieved in 20 patients, a PR in 46 patients, SD in 18 patients, and PD in 0 patients. Thus, the ORR in the TACE group was 78.6% (66/84 patients). The difference in initial treatment efficacy between the two groups did not reach significance (p=0.227).

Univariate and multivariate analyses of factors contributing to OS. Univariate analysis identified the following factors as being significantly associated with OS for all cases (n=150): the Child-Pugh classification (p<0.001), tumor number of ≤5 (p=0.001), tumor distribution (p=0.001), maximum tumor size of ≤4.5 cm (p=0.008), objective tumor response at initial treatment (p=0.004), serum albumin level of ≥3.7 g/dl (p=0.014), and total bilirubin level of ≥1.0 mg/dl (p=0.011) (Table II). The hazard ratios and 95% confidence intervals calculated using multivariate analysis for the eight factors with p-values of <0.05 in the univariate analysis are detailed in Table II. The Child-Pugh classification (p=0.039), tumor number of ≤5 (p=0.018), maximum tumor size of ≤4.5 cm (p=0.048), and ORR at initial therapy (p=0.010) were found to be significant predictors linked to OS in multivariate analysis.

Causes of death. Thirty-two patients in the elderly group (48.5%) died during the follow-up period. The causes of death were HCC progression in 24 patients, liver failure in 4 patients, and miscellaneous causes in 4 patients. Fifty-two patients in the control group (61.9%) died during the follow-up period, and the causes of death were HCC progression in 29 patients, liver failure in 19 patients, and miscellaneous causes in 4 patients.

Adverse events and hospitalization days in the two groups. In both groups, symptoms associated with postembolization syndrome such as fever, appetite loss, abdominal pain, and nausea were transient and mostly resolved within 2 weeks after initial treatment (35). In the elderly group, serious adverse events (SAEs) were observed in three patients (4.5%). Each of these three patients had one of the following SAEs: cholangitis, aspiration pneumonia, or liver abscess formation. All of these SAEs were managed successfully. Thus, TACE-related mortality in the elderly group was 0%. In the control group, SAEs were observed in five patients (6.0%). Each of these five patients had one of the following SAEs: acute respiratory distress syndrome (ARDS), hepatic encephalopathy, hyponatremia, hyperbilirubinemia, or refractory ascites. All of these SAEs were managed successfully, although in one patient who developed ARDS, management in the intensive care unit was required. Thus, TACE-related mortality in the control group was 0%. The mean number of hospitalization days in the elderly group tended to be less than that in the control group (10.7 ± 5.0 *vs.* 12.6 ± 6.7 days, respectively; p=0.053).

Table II. Univariate and multivariate analysis contributing to overall survival.

Variables	n	Univariate Analysis	Multivariate Analysis	
			Hazard Ratio (95% CI)	*P* value[a]
Gender, male *vs.* female	97 / 53	0.952		
Age (years), ≥75 *vs.* <75	66 / 84	0.887		
Child-Pugh, A *vs.* B	105 / 45	<0.001	0.524 (0.283-0.969)	0.039
Tumor number, >5 *vs.* ≤5	35 / 115	0.001	0.489 (0.270-0.885)	0.018
Tumor distribution, bilobar *vs.* unilobar	60 / 90	0.001	1.128 (0.632-2.016)	0.683
Maximum tumor size, ≥4.5cm *vs.* <4.5cm	73 / 77	0.008	0.633 (0.402-0.996)	0.048
Objective response at initial therapy, yes / no	120 / 30	0.004	2.017(1.180-3.448)	0.010
AST (IU / L), ≥50 *vs.* < 50	83 / 67	0.188		
ALT (IU / L), ≥ 40 *vs.* < 40	77 / 73	0.992		
ALP (IU / L), ≥ 360 *vs.* < 360	73 / 77	0.060		
GGT (IU / L), ≥ 80 *vs.* < 80	73 / 77	0.322		
Serum albumin level (g / dL), ≥3.7 *vs.* <3.7	74 / 76	0.014	1.219 (0.690-2.154)	0.496
Total bilirubin (mg / dL), ≥1.0 *vs.* <1.0	59 / 91	0.011	0.766 (0.472-1.243)	0.281
Platelet count ($\times 10^4$ / mm^3), ≥13 *vs.* <13	73 / 77	0.937		
Prothrombin time (%), ≥87 *vs.* <87	73 / 77	0.070		
Serum creatinine (mg / dL), ≥1.0 *vs.* <1.0	45 / 105	0.926		
Diabetes mellitus, yes/no	54/96	0.423		
Body mass index (kg/m^2), ≥23 vs. <23	74/76	0.835		
Serum AFP (ng / mL), ≥40 *vs.* <40	72 / 78	0.166		
DCP (mAU / mL), ≥800 *vs.* <800	79 / 71	0.069		

CI; confidence interval, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin, [a] Cox proportional hazard model.

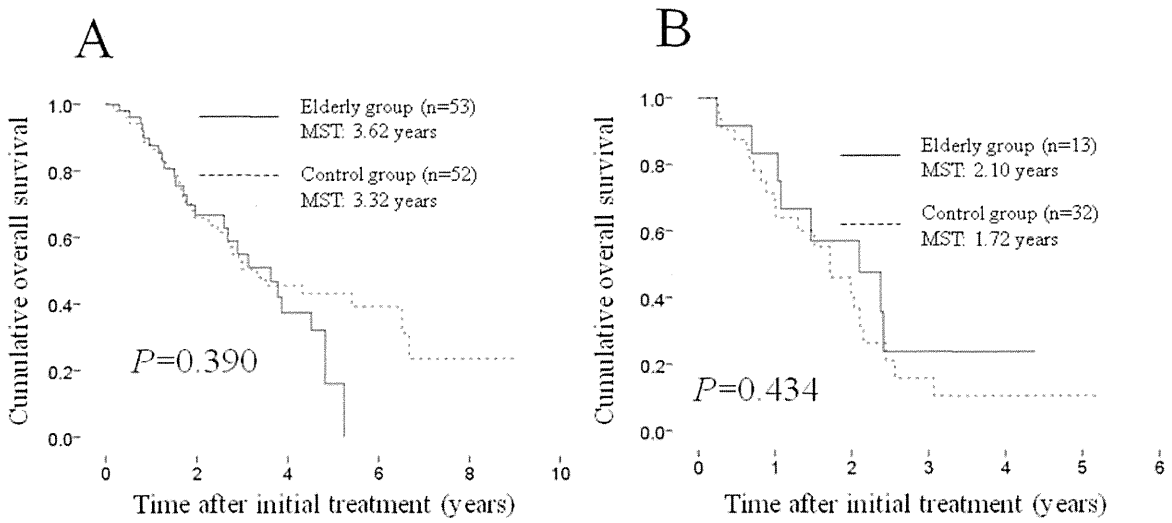

Figure 2. Subgroup analyses according to the Child-Pugh classification. No significant difference (p=0.390) was observed between the two groups in terms of OS in patients with Child-Pugh class A disease (53 patients [80.3%] in the elderly group and 52 [61.9%] in the control group); the MST was 3.62 years in the elderly group and 3.32 years in the control group (A). Similarly, there was no significant difference (p=0.434) between the two groups in terms of OS in patients with Child-Pugh class B disease (13 patients [19.7%] in the elderly group and 32 [38.1%] in the control group); the MST was 2.10 years in the elderly group and 1.72 years in the control group (B). MST: median survival time.

Subgroup analyses according to the Child-Pugh classification. A significant difference was observed between the two groups in terms of the Child-Pugh classification (p=0.019), and we therefore performed subgroup analyses according to this classification. No significant difference (p=0.390) was observed between the two groups in terms of OS in patients with Child-Pugh class A disease (53 patients [80.3%] in the elderly group and 52 patients [61.9%] in the control group); the MST was 3.62 years in the elderly group and 3.32 years in the control group (Figure 2A). Similarly, no significant difference (p=0.434) was found between the two groups in terms of OS in patients with Child-Pugh class B disease (13 patients [19.7%] in the elderly group and 32 [38.1%] in the control group); the MST was 2.10 years in the elderly group and 1.72 years in the control group (Figure 2B).

Subgroup analyses according to maximum tumor size. Although there were no significant differences in baseline tumor characteristics between the two groups, tumor-related characteristics are reportedly prognostic factors associated with OS in patients with

HCC undergoing TACE (8, 15-17). Hence, we performed subgroup analyses according to maximum tumor size. No significant difference (p=0.861) was observed between the two groups in terms OS in patients with a maximum tumor size of ≥4.5 cm (39 patients [59.1%] in the elderly group and 38 [45.2%] in the control group); the MST was 2.41 years in the elderly group and 1.88 years in the control group (Figure 3A). Similarly, no significant difference (p=0.559) was found between the two groups in terms of OS in patients with a maximum tumor size of <4.5 cm (27 patients [40.9%] in the elderly group and 46 [54.8%] in the control group); the MST was 3.78 years in the elderly group and 2.92 years in the control group (Figure 3B).

Subgroup analyses according to gender and other factors. Since a significant difference of proportion of male patients was observed between the two groups, we performed subgroup analyses according to gender. In male patients (34 patients in the elderly group and 63 in the control group), the MST was 2.68 years in the elderly group and 2.56 years in the control group (p=0.986). In female patients (32 patients in the elderly group and 21 in the control group), the MST was 3.62 years in the elderly group and 2.10 years in the control group (p=0.885). In subgroup analyses of other factors [tumor number (>5 or ≤5), presence or absence of ORR, tumor distribution (bilobar or unilobar), pretreatment serum albumin level (≥3.7g/dl or <3.7g/dl) and total bilirubin (≥1mg/dl or <1mg/dl)], no significant difference was observed in the two groups in terms of OS (data not shown).

Discussion

In Japan, there is a trend toward an increasing number of elderly patients with HCC. In addition, the latest estimates suggest that the incidence of HCC peaks above the age of 70 years worldwide (36). However, few investigators have reported the clinical outcome in elderly patients with intermediate-stage HCC who underwent TACE as initial therapy, although there are several studies on the clinical outcome in elderly patients with HCC who underwent surgical resection or ablative therapies (21, 23-26, 37-47). Hence, we conducted the current comparative study.

Our results showed no significant difference in OS or treatment efficacy at initial therapy between the elderly group and the control group, and similar results were obtained in all subgroup analyses. These findings indicate that elderly patients with intermediate-stage HCC who underwent TACE had a prognosis comparable with that of younger patients. Cohen et al. reported that the MST in patients with HCC aged ≥75 years treated with TACE was 1.88 years, while in our study, the MST in the elderly group was 2.90 years (25). Because the baseline characteristics differed between their study and ours, it may not be possible to reach a definitive conclusion. However, our TACE procedure may have been more effective than that of Cohen et al.

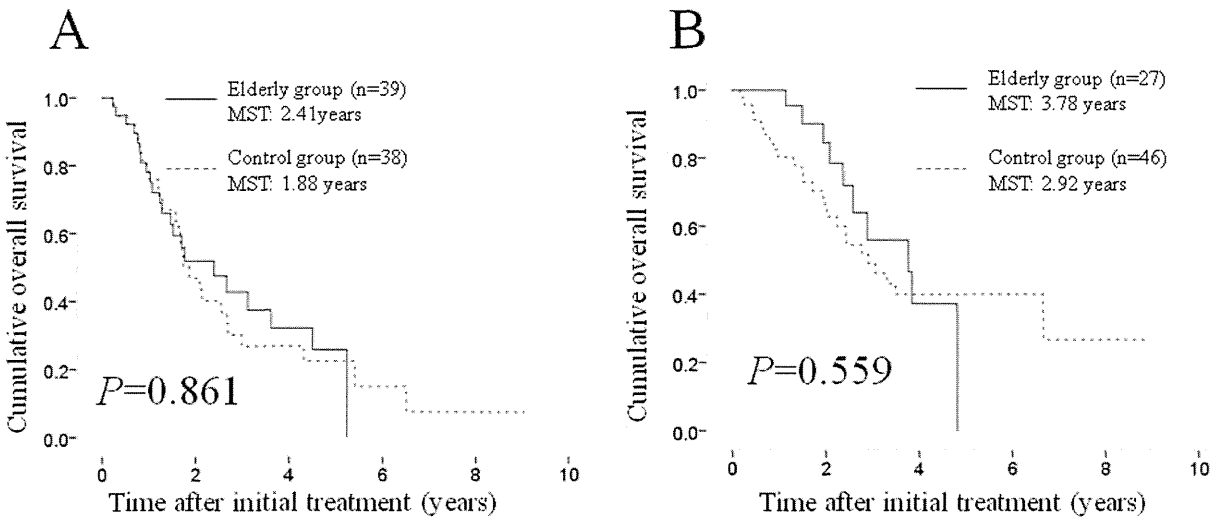

Figure 3. Subgroup analyses according to maximum tumor size. No significant difference (p=0.861) was observed between the two groups in terms of OS in patients with a maximum tumor size of ≥4.5 cm (39 patients [59.1%] in the elderly group and 38 [45.2%] in the control group); the MST was 2.41 years in the elderly group and 1.88 years in the control group (A). Similarly, there was no significant difference (p=0.559) between the two groups in terms of OS in patients with a maximum tumor size of <4.5 cm (27 patients [40.9%] in the elderly group and 46 [54.8%] in the control group); the MST was 3.78 years in the elderly group and 2.92 years in the control group (B). MST: median survival time.

In the present study, a significantly higher proportion of female patients and a lower positivity rate for hepatitis B surface antigen were found in the elderly group than in the control group and patients in the elderly group had a liver functional reserve superior to that of patients in the control group. In previous studies, elderly patients with HCC were more likely to be women (37–47). This may have been associated with a larger female elderly population because of their longer life expectancy (39). The fact that male tend to drink and smoke more than female in general may also be associated with our observations, although in this study, drinking history and smoking history are not exactly taken from all studied subjects. Furthermore, as in our study, elderly patients with HCC were more likely to have hepatitis C virus (HCV) than hepatitis B virus (HBV) carriers in many previous studies (37-47). This finding may be explained by the fact that most HBV carriers acquire the virus via vertical transmission in the perinatal period, whereas most HCV carriers are infected at a later stage in life. HCC therefore manifests as a complication in HCV carriers much later in life than in HBV carriers (40–47). Interestingly, however, the elderly group had a significantly lower BMI than that of the control group. Hepatic steatosis is significantly correlated with an increasing BMI and results in accelerated liver carcinogenesis (48–50). These facts may be related to our observations.

In our multivariate analysis, the Child-Pugh classification, tumor number of ≤5, maximum tumor size of ≤4.5cm, and ORR at initial therapy were significant predictors associated with OS. Takayasu et al. reported in their large study that the degree of liver damage, alpha-fetoprotein level, maximum tumor size, number of lesions, and degree of portal vein invasion were significant factors linked to OS according to their multivariate analysis (8). Our results are consistent with their reports.

In general, elderly patients have a significantly higher proportion of comorbid diseases than younger patients (24, 25, 37–47) However, our baseline characteristics showed no significant difference in comorbid diseases between the two groups. Elderly patients with HCC with severe or numerous comorbid diseases may be excluded from the current analysis because of the expected TACE-related SAEs. The fact that the proportion of patients with Child-Pugh B disease was significantly lower in the elderly group than in the control group may be also due to the same reason.

In our study, TACE-related mortality was 0% in both groups. TACE-related mortality reportedly ranges from 0.5% to 7% (8, 21, 23). Furthermore, the mean number of hospitalization days in the elderly group tended to be fewer than that in the control group. Our safety profile of TACE in elderly patients with HCC is encouraging.

This study had several limitations. First, it was a retrospective study over the period of 10 years. Thus, diagnostic procedure and treatment procedure for HCC may not be consistent in each patient, leading to bias. Second, the sample sizes in the two cohorts were small for analysis. Third, as mentioned earlier, elderly patients with severe comorbid diseases may be excluded from this analysis, also potentially leading to bias. Larger prospective comparative studies will therefore be needed in the future to confirm these results. However, our study results demonstrated that the elderly group had a prognosis comparable with that in the control group and that our TACE procedure was safe.

In conclusion, elderly patients with intermediate-stage HCC undergoing TACE had a prognosis comparable with that of younger patients with intermediate-stage HCC undergoing TACE. TACE for elderly patients with intermediate-stage HCC should not be withheld based on advanced age alone.

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Competing Interests

The authors have not received any financial support for this study and have no conflicts of interest to declare.

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Review

Transcatheter Arterial Embolic Therapies for Hepatocellular Carcinoma: A Literature Review

HIROKI NISHIKAWA, RYUICHI KITA, TORU KIMURA AND YUKIO OSAKI

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Abstract. *Palliative therapies for hepatocellular carcinoma (HCC) include transcatheter arterial embolic therapies, radiation therapy and systemic chemotherapies such as sorafenib. Conventional transcatheter arterial chemoembolization (cTACE) is the golden standard for the treatment of intermediate-stage HCC, and involves the administration of chemotherapuetic drugs, with or without lipiodol, by means of a catheter directly to the feeding artery of the targeted tumor followed by the administration of embolic agents, while the concept of drug-eluting bead TACE (DEB-TACE) builds on the rationale for cTACE. DEB-TACE has been demonstrated to substantially improve the pharmacokinetic profile of TACE, providing levels of consistency and repeatability in patients which are not available with cTACE. On the other hand, the technique of radioembolization therapy for HCC involves the delivery of high-dose radiation via the hepatic artery. In this review, we summarize the current status of these transcatheter arterial embolic therapies in HCC.*

Hepatocellular carcinoma (HCC) continues to represent a major health problem worldwide (1, 2). While treatment options for HCC such as surgical resection (SR), liver transplantation (LT) and ablative therapies may provide a chance for cure, these are often precluded due to advanced disease presentation or poor liver functional reserve (1, 2). Late-stage HCC presentation, severe co-morbidities, and limited donor availability enables fewer than 20% of patients to receive curative therapies for HCC. Palliative therapies include transcatheter arterial embolic therapies, radiation therapy and systemic chemotherapies such as sorafenib. (1-3) Transcatheter arterial chemoembolization (TACE) is a procedure whereby an embolic agent is injected into the tumor-feeding artery to deprive it of its major nutrient source by means of embolization; this results in ischemic necrosis of the targeted tumor (4-6). The circulation of the liver is unique due to the dual blood supply by the hepatic artery and portal vein. The portal vein is responsible for about 80% of the blood supply to normal liver tissue, while 99% of the blood supply to hepatic tumors is delivered by the hepatic artery (4-7). These differences in blood supply to HCC tumor and the liver form the theoretical basis of transcatheter arterial therapy for HCC.

The ideal TACE procedure for HCC should allow maximum and sustained concentration of anticancer drug in the tumor, with minimal systemic exposure combined with calibrated tumor feeding vessel obstruction. While the concept of drug-eluting bead TACE (DEB-TACE) builds on the rationale for conventional TACE (cTACE) (4, 5, 8-10). The European Association for the Study of the Liver (EASL) guidelines recommend TACE for unresectable, Child-Pugh A or B multiple HCC with no vascular invasion [BCLC-B stage (intermediate-stage) HCC]. About 20% of patients with HCC are classified as having intermediate-stage HCC, and present a 2-year survival of around 50% (11). The technique of radioembolization therapy for HCC involves the delivery of high-dose radiation *via* the hepatic artery and this technique represents an alternate form of therapy for BCLC-B HCC (12-14). However, on the other hand, in terms of chemotherapeutic agents used for TACE in HCC therapy, there are currently no global guidelines with regard to the optimal dose, choice or combination of cytotoxic agents for TACE. Thus, it is difficult to compare data between different TACE studies. TACE has also been performed as preoperative (prior to SR or LT) adjuvant chemotherapy in patients with HCC with the aim of improving survival, preventing dropout from waiting list for LT and down-staging of HCC before LT, which means bridging therapy for LT.

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Key Words: Hepatocellular carcinoma, transcatheter arterial chemoembolization, radioembolization, combination therapy, review.

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In this review, based on the existing literatures we summarize the current status of these transcatheter arterial embolic therapies in HCC, as well as discussing related topics including choice of chemotherapeutic agents, bridging therapy for SR or LT and combination therapies.

Indications and Contraindications for TACE

The EASL guidelines recommend TACE for unresectable, Child-Pugh A or B multiple HCC with no vascular invasion while in Japan the therapy is recommended even for HCC with vascular invasion if it is Vp1 (tumor invasion to peripheral site than the second branch of portal vein) or Vp2 (tumor invasion to the second branch of portal vein) (11, 15). Liver function is a critical component for careful patient selection for TACE. While patients with absolute contraindication for TACE include those with decompensated liver cirrhosis, severely reduced portal vein flow due to nontumoral portal vein occlusion or hepatofugal blood flow, extensive tumor with massive replacement of both lobes, technical contraindications to transcatheter arterial therapies (*e.g.* untreatable arterio-venous shunt) or severe comorbidities involving compromised organ function such as renal deficiency (16).

Choice of Chemotherapeutic Drug for TACE and Comparison Between Different Treatment Regimens in TACE for HCC

Worldwide, the most popular anticancer agent for TACE in patients with HCC is doxorubicin (4). In Japan, epirubicin, mitomycin, cisplatin and miriplatin, a cisplatin derivative (Miripla; Dainippon Sumitomo Co., Ltd., Tokyo, Japan), have also been used for TACE as chemotherapeutic agents (17, 18). However, there is no clear consensus regarding the optimal chemotherapeutic drug to use in cTACE. Sahara *et al.* conducted a randomized control trial (RCT) for comparing the safety and short-term efficacy of TACE using cisplatin-lipiodol suspension (n=12) with that using epirubicin-lipiodol emulsion (n=16) in patients with recurrent HCC and demonstrated that no significant difference was found with regard to adverse effects, the treatment effect on HCC nodules, or overall tumor response in the two groups (19). Yodono *et al.* retrospectively examined clinical outcome in 202 HCC patients treated with TACE using either epirubicin-lipiodol emulsion (n=106) or a fine-powder formulation of cisplatin-lipiodol suspension (n=96) and reported that TACE using a gelatin sponge and lipiodol with cisplatin led to better progression-free and overall survival (OS) rates than TACE with the epirubicin-lipiodol emulsion in patients with HCC (20). On the other hand, Oguro *et al.* retrospectively investigated the short-term therapeutic effects and adverse effects associated with the use of miriplatin-lipiodol suspension for TACE in patients with HCC (n=48), using TACE with cisplatin-lipiodol suspension as the historical control (n=50), and demonstrated that TACE using miriplatin-lipiodol suspension yielded worse short-term responses than did cisplatin-lipiodol suspension, although the rates of adverse events were significantly lower in the miriplatin-lipiodol-treated group (21). Handa *et al.* retrospectively compared the treatment efficacy of TACE using miriplatin in patients with HCC (n=124) and that using epirubicin (n=97). They concluded that although miriplatin-TACE was superior to epirubicin-TACE in the short term, it proved inferior to the latter in the long term (22). In view of these results, as mentioned earlier, the optimal chemotherapeutic agent for HCC treatment with TACE remains unclear. Further studies will be thus needed to reach definitive conclusion. Previous reports regarding comparison between different chemotherapeutic regimens for TACE in HCC are listed in Table I.

Improving Treatment Efficacy of TACE (Superselective TACE and Warmed Miriplatin)

Superselective TACE is defined as TACE from the distal portion of the feeding subsegmental hepatic artery to evoke severe ischemic effects on a small, limited area of the liver, thus avoiding damage to liver functional reserve; common complications of this technique are mild fever, mild pain and temporary minimal changes of liver function (26). Several investigators reported that using this technique, approximately 40-70% of patients with HCC with tumors sized <4-5 cm can obtain complete tumor necrosis or remain local tumor progression free for more than three years after superselective TACE (27). However, there is a problem that this technique highly depends on the skill of the operator.

Miriplatin is a novel chemotherapeutic drug designed for use in transarterial infusion chemotherapy with or without embolization for HCC (28). Miriplatin: (i) inhibits cell proliferation in a similar fashion to cisplatin and has superior solubility in ethyl esters of iodized fatty acids derived from poppy seed oil; (ii) releases its platinum constituent continuously, together with the ethyl esters (sustained release), by remaining at the site of the tumor; and (iii) has fewer side effects, because of its sustained release and its minimal presence in the general circulation (29, 30). In Japan, miriplatin was approved for use in October 2009. Seko *et al.* investigated the difference in antitumor efficacy between patients who underwent TACE for HCC using warmed (40°C) miriplatin (n=45) and those treated using room temperature miriplatin (n=158). (31) In their results, 17 patients (44.3%) treated with room temperature miriplatin and 32 patients (71.1%) with warmed miriplatin experienced complete or partial responses. Thus, they concluded that warmed miriplatin can be considered as one of the standard

Table I. *Previous reports regarding comparison between different chemotherapeutic regimens for conventional transcatheter arterial chemoembolization in hepatocellular carcinoma.*

Author	Country	Year	Chemotherapeutic drug	Design	n	Treatment efficacy	Local recurrence	Survival
Ueda, *et al.* (23)	Japan	2013	Cisplatin *vs.* miriplatin	Retro	25 *vs.* 21	ORR: 81% *vs.* 50% (p=0.011)	NA	NA
Handa, *et al.* (22)	Japan	2013	Epirubicin *vs.* n miriplati	Retro	97 *vs.* 124	TE4: 33.0% *vs.* 46.8%	43.1% *vs.* 71.2% at 18 months	NA
Aramaki, *et al.* (24)	Japan	2013	Epirubicin *vs.* miriplatin	Retro	42 *vs.* 27	ORR: 85.7% *vs.* 81.5%	TTP: 5.1 months *vs.* 7.5 months	NA
Oguro, *et al.* (21)	Japan	2012	Cisplatin *vs.* miriplatin	Retro	50 *vs.* 48	ORR: 86.0% *vs.* 56.3%	NA	NA
Yodono, *et al.* (20)	Japan	2011	Epirubicin *vs.* cisplatin	Retro	106 *vs.* 96	NA	NA	3-Year OS: 36.5% *vs.* 62.4% (p=0.0052)
Yamanaka, *et al.* (25)	Japan	2011	Epirubicin *vs.* cisplatin	Retro	99 *vs.* 32	ORR: 51.5% *vs.* 62.5%	NA	NA
Sahara, *et al.* (19)	Japan	2010	Epirubicin *vs.* cisplatin	RCT	16 *vs.* 12	ORR: 37.5% *vs.* 50.0% (p=0.615)	NA	NA

ORR: Objective response rate; retro: retrospective study; RCT: randomized controlled trial; TTP: time to progression; OS: overall survival; NA: not available. TE4 (treatment effect 4), radiologic complete response.

treatments for unresectable HCC in patients who are eligible for TACE (31). Their favorable results of warmed miriplatin for TACE may be associated with reduced viscosity and injection pressure through microcatheters of miriplatin-lipiodol suspension (31, 32).

Assessment of Treatment Response, Treatment Schedule and Definition of TACE Failure

Assessment of tumor response is important in patients undergoing TACE for HCC as it is associated with clinical outcome (4, 18, 20). However, unfortunately, conventional methods for tumor response evaluation, such as Response Evaluation Criteria in Solid Tumors (RECIST), have no predictive value in HCC patients who underwent TACE because these criteria only rely on tumor shrinkage as a measure of anticancer activity (3, 11, 33). As mentioned above, TACE for HCC is a procedure whereby an embolic agent is injected into the tumor feeding artery to deprive it of its major nutrient source by means of embolization and this results in direct ischemic necrosis of the targeted HCC tumor. Its antitumor effect is not paralleled by a reduction in overall tumor load but rather by a reduction in viable tumor, as identified by imaging modalities such as contrast-enhanced computed tomography (CT). Modified RECIST (mRECIST) for HCC therapy is based on the fact that diameter of the targeted HCC tumors with viable tumor should guide all measurements (34). Tumor response assessed by mRECIST after TACE therapy for HCC has been demonstrated to correlate well with survival (35). The recent Clinical Practice Guidelines jointly issued by the EASL and the European Organization for Research and Treatment of Cancer recommend that assessment of treatment response in HCC therapy should be based on mRECIST criteria by performing contrast-enhanced CT or magnetic resonance imaging (MRI) 4 weeks after initial therapy for HCC (11). On the other hand, TACE has been performed both at regular predefined time intervals (every 2 to 8 months in general) and on demand according to treatment response as assessed by imaging modalities (on-demand TACE) (5). However, no RCTs have been conducted to investigate the optimal frequency of TACE therapy. In Japan, on-demand TACE is common and further TACE treatment is usually considered in patients with residual viable HCC tumor at 8 to 12 weeks after the initial treatment (6).

Patients with HCC treated with TACE often have unfavorable clinical outcomes with repeated TACE and there is considerable uncertainty surrounding the criteria for repeating or discontinuing TACE therapy. It is important to provide a clearer indication of when TACE should be repeated and more importantly, when TACE should be stopped. An Expert Panel Opinion on Interventions in Hepatocellular Carcinoma recommended the following: (i) TACE should be performed on demand and the decision to repeat TACE should be based not only on treatment response or tumor progression but also on the patient's clinical conditions and tolerance, which should be evaluated before each new cycle of TACE; (ii) HCC stage progression such as the development of vascular invasion or extrahepatic spread during follow-up may provide a useful surrogate measure of refractoriness to TACE; (iii) In clinical practice, three sessions of TACE (within 6 months) should be adequate for effective tumor control and

patients without effective tumor control after these procedures should be regarded as having TACE refractory disease (36). On the other hand, several investigators proposed that Assessment for Retreatment with TACE score (ART score) as assessed by the increase of aspartate aminotransferase by >25% from baseline, an increase of Child-Pugh score of 1 or more than 1 point from baseline, and the absence of radiologic tumor response is useful for predicting refractoriness to TACE and a score of 2.5 or more prior to the second TACE identifies patients with a dismal prognosis who may not benefit from further TACE sessions (37, 38).

Intermediate-stage HCC: Comparison of TACE and Other Therapies Regarding survival

The BCLC intermediate stage, or BCLC-B, includes patients with Child-Pugh A and B with large, single-focus HCC (>5 cm) and patients with multifocal HCC, defined as more than three tumors of any size, or 2-3 tumors with a maximal diameter greater than 3 cm. To be categorized as having BCLC-B HCC, patients should be asymptomatic and have no vascular invasion or extrahepatic spread. The BCLC classification indicates that these patients are optimal candidates for TACE (3). However, the BCLC-B stage includes patients varying widely in tumor stage, liver function (Child-Pugh A or B), performance status 0-2 and etiology of underlying liver disease. TACE may thus not be the optimal therapy for all of them. Some patients with intermediate-stage HCC may benefit from other treatment options, which are currently approved or being explored.

Zhong *et al.* reported that out of a total of 257 and 135 BCLC-B patients with HCC undergoing SR and TACE, the SR group had significantly higher OS rates than the TACE group (1 year, 87% *vs.* 77%; 3 years, 62% *vs.* 44%; 5 years, 35% *vs.* 20%; p=0.025) after propensity score matching adjusting for possible variables associated with survival (39). Similarly, Hsu, *et al.* demonstrated that in a total of 268 and 455 patients with, the 1-, 3- and 5- year survival rates of HCC patients undergoing SR and TACE were 82% *vs.* 65%, 68% *vs.* 29% and 46% *vs.* 22%, respectively, in the propensity score matching model (146 pairs, p<0.001) (40). In view of these results, SR for intermediate-stage HCC can be a treatment option for some selected patients. On the other hand, Zhao *et al.* compared clinical outcome between patients treated with TACE and those treated with TACE plus radiofrequency ablation (RFA) in intermediate or advanced HCC (n=167) (41). They concluded that the treatment regimen of TACE plus RFA has the advantages of tumor control, liver function protection and survival extending in the treatment of HCC compared with TACE alone in intermediate or advanced stage HCC (41).

The introduction of sorafenib in the therapeutic armamentarium for HCC has provided a new treatment option for the treatment of patients with intermediate-stage HCC for whom TACE is unsuitable due to anatomical reasons or in whom TACE resulted in unacceptable toxicity. Based on available evidence, sorafenib has a role in patients with HCC who fail or are not eligible for TACE (16). Bruix *et al.* performed a subgroup analysis of the landmark SHARP study to examine the efficacy of sorafenib in patients with intermediate-stage HCC (sorafenib group, n=54; placebo group, n=51) (42). They demonstrated that patients treated with sorafenib had a longer median OS [14.5 *vs.* 11.4 months, hazard ratio (HR) =0.72], time to progression (TTP) (6.9 *vs.* 4.4 months, HR=0.47) and a higher disease control rate (50.0% *vs.* 43.1%) than those who received placebo (42).

Conventional TACE and DEB-TACE

Transcatheter arterial embolization was initially used to treat HCC by Doyon *et al.* in 1974 and was applied to most unresectable HCC using gelatin sponge particles and anticancer agents by Yamada *et al.* in Japan. (43, 44) In the 1980s, TACE was the only non-surgical therapy for unresectable HCC until the introduction of percutaneous ethanol injection therapy for HCC. In the mid-1990s, lipiodol was newly introduced to enhance mainly the therapeutic effect. It is a substance which is selectively retained within tumor and increases chemotherapeutic exposure as a drug carrier (45, 46). Lipiodol permits the anticancer drug to concentrate in the targeted tumor and is retained for weeks, while in normal hepatocytes excretion is around seven days. The antitumor efficacy of TACE using lipiodol emulsion is higher than that of anticancer drugs and iodized oil when administered alone (44-49). TACE using lipiodol emulsion for unresectable HCC (*i.e.* conventional TACE) has thus been gaining popularity.

Survival benefits obtained by TACE were demonstrated in two RCTs. In 2002, Llovet *et al.* demonstrated in their RCT that TACE had survival benefits compared with conservative treatment [HR=0.47, 95% confidence interval (CI), 0.25-0.91, p=0.025] (50). Similarly, in 2002, Lo *et al.* demonstrated in their RCT that TACE resulted in a marked tumor response, and the 1-, 2- and 3- year survival rates were significantly better in the TACE group (57%, 31% and 26%, respectively) than in the control group (32%, 11% and 3%, respectively, p=0.002) (51). On the other hand, the survival benefit of TACE has been examined in other RCTs, and two of these did not show a prolonged survival time as compared with control group of patients (52, 53). However, in 2003, Llovet *et al.* conducted a meta analysis of transcatheter arterial embolization or TACE for HCC (seven trials, 545 patients) and reported that both transcatheter arterial embolization and TACE improved 2-year survival compared with the control group with best supportive care (HR=0.53,

95% CI=0.32-0.89, p=0.017). (54) Currently, the EASL guidelines recommend TACE for intermediate stage HCC while in Japan the therapy is recommended even for HCC with vascular invasion if it is Vp1 or Vp2 (11, 15).

TACE-related adverse events are transient and manageable in general, however, they can occur in a significant proportion of individuals (30-100%) (5, 6, 16). They include ascites, deterioration of liver function, infection such as liver abscess, gastrointestinal bleeding and post-embolization syndrome comprising fever and abdominal pain (5, 6, 16). In summary, conventional TACE may be associated with some survival benefits. However, since the level of survival benefits from conventional TACE varies, a careful selection of patients with HCC may be crucial.

DEB-TACE uses doxorubicin-loaded beads rather than the conventional doxorubicin-lipiodol emulsion (4, 5). DEB-TACE ensures sustained and slow release of the chemotherapeutic drug locally in addition to causing ischemic injury to the tumor and it has been shown that this treatment modality can result in an overall favorable toxicity profile and anticancer efficacy. (4, 5) In 2010, Lammer *et al.* in their RCT (PRECISION V trial) compared DEB-TACE with cTACE for the treatment of 212 cirrhotic patients with HCC and found that the DEB-TACE group had higher rates of complete response, objective response and disease control as compared with the cTACE group. In subgroup analyses of patients with Child-Pugh B, PS 1, bilobar disease and recurrent disease, the DEB-TACE group exhibited significantly higher response rates and DEB-TACE was associated with a reduction in serious liver toxicity and a lower rate of doxorubicin-related side-effects as compared with cTACE. (8) In 2010, in their RCT which compared DEB-TACE with doxorubicin (n=41) and bland transcatheter arterial embolization (transcatheter arterial embolic therapy without chemolization) with BeadBlock (n=43), Malagari *et al.* reported that at six months, objective response rates were 73.2% (30/41) in the DEB-TACE group and 55.8% (24/43) in the bland transcatheter arterial embolization group, HCC recurrence rate was higher for the bland transcatheter arterial embolization group (78.3% *vs.* 45.7%) at 12 months, but TTP was longer for the DEB-TACE group (42.4 weeks *vs.* 36.2 weeks, p=0.008) (9). Thus, they concluded that DEB-TACE leads to a better local response, fewer recurrences, and a longer TTP than bland transcatheter arterial embolization with BeadBlock (9). On the other hand, in 2012, Song *et al.* showed in their retrospective study that the treatment response in the DEB-TACE group (n=60) was significantly higher than that of the cTACE group (n=69) (p<0.001) and TTP was significantly longer (11.7 and 7.6 months, respectively, p=0.018), although there was no statistically significant difference in liver toxicity between the groups (p>0.05) (55). Furthermore, Martin *et al.* (56) and Huang *et al.* (57) in their meta analyses demonstrated that DEB-TACE is an effective therapy with a favorable pharmacokinetic profile with significantly less systemic doxorubicin exposure when compared to cTACE. In view of these results, DEB-TACE may be associated with an increased response rate and reduced treatment-related toxicity compared with cTACE. DEB-TACE has been increasingly used as the first-line transcatheter arterial embolic therapy for HCC, although phase III trials comparing DEB-TACE and conventional regimens are lacking and the clinical data for DEB-TACE using chemothereapeutic agents other than doxorubicin such as epirubicin, cisplatin and miriplatin frequently used in Japan are also lacking. However, if favorable results are obtained in studies using these regimens, DEB-TACE will likely replace cTACE in the near future. Previous studies regarding comparison between DEB-TACE and cTACE or bland transcatheter arterial embolization in HCC are listed in Table II.

Preoperative TACE Prior to SR or LT

TACE has also been performed as preoperative adjuvant chemotherapy in patients with resectable HCC with the aim of improving survival. (61-66) Four RCTs assessed the efficacy of preoperative TACE in terms of survival. (61-64) Wu *et al.* conducted an RCT in 52 patients with large HCC (n=24 in the pretreatment TACE group and n=28 in the control group), concluding that preoperative TACE for resectable large HCC should be avoided since it does not provide complete necrosis of large HCC tumors and results in delayed surgery and difficulty in the treatment of recurrent lesions without any survival benefit. (64) Yamasaki *et al.* conducted an RCT on 97 patients (solitary HCC, 2-5 cm in size; n=50 in the pretreatment transcatheter arterial embolization group and n=47 in the control group) and demonstrated that preoperative transcatheter arterial embolization did not improve postoperative survival (63). Similarly, Zhou *et al.* (61) and Kaibori *et al.* (62) reported in their RCTs that preoperative TACE did not improve clinical outcomes. In summary, preoperative TACE for HCC may not be associated with improved clinical outcomes.

In patients with HCC on the waiting list for LT, cTACE is the most frequently used therapy before LT for HCC (so-called bridging therapy) since such patients can experience HCC progression beyond the accepted criteria for LT (67, 68). However, due to the small number of prospective studies of cTACE before LT with well-defined entry criteria and the variability of results, the role of cTACE in tumor down-staging is still to be defined. On the other hand, there are several studies comparing outcome of cTACE and DEB-TACE before LT for HCC. Nicolini *et al.* compared recurrence-free survival (RFS) after LT for HCC and effects of HCC necrosis on tumor histology between patients treated with cTACE before LT (n=16) and those treated

Table II. *Previous studies regarding comparison between drug-eluting bead transcatheter arterial chemoembolization and conventional transcatheter arterial chemoembolization or bland transcatheter arterial embolization for hepatocellular carcinoma.*

Author	Country	Year	Design	Treatment	n (DEB *vs.* control)	ORR (DEB *vs.* control)	DCR (DEB *vs.* control)	SAE (DEB *vs.* control)
Lammer, *et al.* (8)	Austria	2010	RCT	DEB-TACE *vs.* cTACE (doxo)	93 *vs.* 108	52% *vs.* 44%	63% *vs.* 52%	23.7% *vs.* 29.6%
Malagari, *et al.* (9)	Greece	2010	RCT	DEB-TACE *vs.* bland TAE	41 *vs.* 43	73.2% *vs.* 55.8%	87.8% *vs.* 79.1%	NA
Wiggermann, *et al.* (58)	Germany	2011	Retro	DEB-TACE *vs.* cTACE (cisplatin)	22 *vs.* 22	22.7% *vs.* 22.7%	90.9% *vs.* 54.5%	13.0% *vs.* 2.3% (p=0.06)
Song, *et al.* (59)	China	2011	Retro	DEB-TACE *vs.* cTACE (doxo)	20 *vs.* 20	85% *vs.* 30% (p=0.001)	NA	NA
Song, *et al.* (55)	China	2012	Retro	DEB-TACE *vs.* cTACE (doxo)	60 *vs.* 69	Better in DEB (p<0.001) TTP: 11.7 *vs.* 7.6 (p=0.018)	NA	NA
Golfieri, *et al.* (60)	Italy	2014	RCT	DEB-TACE *vs.* cTACE (doxo)	89 *vs.* 88	Tumor response: NS TTP: NS	NA	NS

DEB-TACE: Drug-eluting bead transcatheter arterial chemoembolization; cTACE: conventional TACE; doxo: doxorubicin; RCT: randomized controlled trial; retro: retrospective study; TAE: transcatheter arterial embolization; ORR: objective response rate; TTP: time to progression in months; DCR: disease control rate; SAE: serious adverse event; NA: not available (abstract only); NS: not significant.

with DEB-TACE (n=22) (10). They reported that the 3-year RFS was significantly higher in DEB-TACE-treated patients than in cTACE-treated patients (87.4% *vs.* 61.5%, p=0.0493) and fibrotic and inflammatory reactions surrounding the tumor nodule were markedly more common in the DEB-TACE group (p<0.0001 for both), concluding that DEB-TACE can effectively promote HCC necrosis and improves RFS after LT for HCC (10). Frenette *et al.* investigated rates of necrosis and HCC recurrence in 111 consecutive patients with HCC who underwent cTACE (n=76) or DEB-TACE (n=35) before LT and reported that rates of necrosis and HCC recurrence did not differ between groups and dropout from the transplant list was equal for both groups (69). In view of these results, whether DEB-TACE before LT can obtain better tumor necrosis rate and survival merit than cTACE before LT remains unclear. Further studies will be needed to confirm these results.

Radioembolization

Radioembolization or selective internal radiation therapy has recently emerged as a treatment option for intermediate-stage HCC and its role for the treatment of unresectable HCC is still being refined (12-14). For patients with HCC treated with radioembolization, implantable radioactive microspheres are delivered into the feeding arteries of the tumor so that tumor nodules are treated irrespective of their location, number or size (12-14). Radioembolization is distinctly different from external beam radiation therapy. Currently, the most popular radioembolization technique uses microspheres coated with Y90 β-emitting isotope (TheraSphere or SIR Sphere) (12-14). Unlike cTACE or DEB-TACE, arterial occlusion is not the intent with radioembolization.

Salem *et al.* performed a comparative efficacy analysis of cTACE (n=122) and radioembolization (n=123) in patients with HCC (70). They reported that patients with HCC treated with cTACE or radioembolization had similar survival and radioembolization resulted in longer TTP and less toxicity than cTACE (70). There is one interesting report assessing quality of life (QoL) in patients with HCC treated with radioembolization. Salem *et al.* in their prospective study compared health-related QoL in patients treated by cTACE (n=27) or Y90 radioembolization (n=29) for HCC and reported that although Y90 radioembolization was used to treat patients with more advanced disease, those who received radioembolization had significant increased scores in several features of QoL, whereas patients who received cTACE had decreases in QoL scores (71).

Combination Strategies

One limitation of TACE has been the high incidence of HCC recurrence. An increase in plasma vascular endothelial growth factor levels after TACE has been well documented and may be a potential cause of HCC recurrence (72). After TACE, the microenvironment of HCC becomes deranged with increased hypoxia. This leads to an up-regulation in hypoxia inducible factor-1α, which in turn up-regulates vascular endothelial growth factor and increases tumor angiogenesis (72, 73). Based on these observations, there has

been interest in combining antiangiogenic molecular targeted agents such as sorafenib with TACE to reduce post-TACE tumor angiogenesis and improve the treatment efficacy of TACE.

Kudo *et al.* conducted an RCT of sorafenib after TACE to evaluate the efficacy and safety of sorafenib in Japanese and Korean patients with unresectable HCC who responded to TACE (n=458; n=229 in the sorafenib group and n=229 in the placebo group). They reported that sorafenib did not significantly prolong TTP (HR=0.87, 95% CI=0.70-1.09, p=0.252) or OS (HR=1.06, 95% CI=0.69-1.64, p=0.790) in patients who responded to TACE (74). The dosing schedule of sorafenib in relation to TACE is an important factor in this combination therapy. The authors concluded that their study results may have been in part due to delays in starting sorafenib after TACE (74). On the other hand, Sansonno *et al.* demonstrated in their RCT that in 80 HCV-infected patients with BCLC-B HCC who underwent TACE, the median TTP was 9.2 months in the sorafenib-treated group and 4.9 months in the placebo-treated group (HR=2.5, 95% CI=1.66-7.56, p<0.001). (75) Pawlik *et al.* conducted phase II trial of sorafenib combined with concurrent DEB-TACE to evaluate safety and efficacy in patients with advanced HCC (single arm, n=35). They demonstrated that the objective response rate was 58% by EASL criteria and treatment-related toxicity was manageable with dose adjustment of sorafenib (76). In their meta analysis to assess the safety and efficacy of combination therapy of sorafenib and TACE in patients with unresectable HCC, Liu *et al.* reported that although the HR for TTP was 0.76 (95% CI=0.66-0.89, p<0.001), and the HR for OS was 0.81 (95% CI=0.65-1.01, p=0.061), concluding that combination therapy of sorafenib and TACE may bring benefits for patients with unresectable HCC in terms of TTP but not OS (77).

To date, more than 20 clinical trials of combined TACE and sorafenib have been reported. One major drawback is that the most noteworthy feature among these studies was the heterogeneous disease statuses of the target populations in terms of baseline liver function, HCC stage and background liver disease, and assessment method of treatment efficacy and TACE procedure may be different between these studies. Furthermore, there are three study designs to combine TACE and sorafenib: (i) an interrupted design where sorafenib is stopped around the time of TACE; (ii) a sequential design where several cycles of TACE are performed first and then sorafenib is initiated; and (iii) a continuous design where both are applied together (36). The results of clinical outcomes of these combination studies are eagerly awaited.

Conclusion

We reviewed transcatheter arterial embolic therapies for HCC based on the existing literatures. Overall, cTACE, DEB-TACE and radioembolization have gained widespread recognition for the treatment of HCC. However, several issues including choice of chemotherapeutic drug for the treatment of embolic therapies for HCC, combination of embolic therapies and molecular targeted agents, and optimal timing transferring from embolic therapy to other therapies remain to be unsolved. By further well-defined studies, these should be addressed in the future.

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