

Comparison of transcatheter arterial chemoembolization and transcatheter arterial chemotherapy infusion for patients with intermediate-stage hepatocellular carcinoma

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Abstract. The aim of the present study was to compare clinical outcomes in patients with intermediate-stage hepatocellular carcinoma (HCC) who underwent the following treatments: transcatheter arterial chemoembolization (TACE) using an epirubicin-mitomycin-lipiodol (EML) emulsion at initial therapy (TACE group; n=145), and transcatheter chemotherapy infusion (TACI) using an EML emulsion at initial therapy (TACI group; n=81). Overall survival (OS) and treatment efficacy in the TACE and TACI groups were retrospectively compared. Prognostic factors associated with OS were examined using univariate and multivariate analyses. Treatment-related mortality was also calculated. The median observation periods were 1.8 years (range, 0.2-9.0 years) in the TACE group and 2.0 years (range, 0.2-8.7 years) in the TACI group. The median survival time and the 1-, 2-, 3- and 5-year cumulative OS rates were 2.68 years and 81.5, 63.4, 43.9 and 32.7%, respectively, in the TACE group, and 2.64 years and 85.0, 60.0, 43.2 and 26.0%, respectively, in the TACI group (P=0.691). The objective response rate was significantly higher in the TACE group compared to the TACI group (80.0 vs. 66.7%; P=0.009). Using multivariate analysis, the Child-Pugh classification (P=0.017), tumor number ≤ 5 (P=0.045) and des- γ -carboxy prothrombin level >100 mAU/ml (P=0.002) were found to be significant predictors linked to OS. In all subgroup analyses involving Child-Pugh classification, maximum tumor size and tumor distribution, the differences in

the two groups did not reach statistical significance in terms of OS. Treatment mortality was 0% in the two groups. In conclusion, patients with intermediate-stage HCC had a comparable prognosis when treated with TACI or TACE.

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 mortality (1-3). The prognosis for untreated HCC is generally poor and the curative treatments for this disease consist of surgical resection, radiofrequency ablation and liver transplantation (1-3). Non-curative therapies for HCC include transcatheter arterial chemoembolization (TACE), transcatheter arterial chemotherapy infusion (TACI), continuous arterial chemoinfusion therapy, radioembolization, molecular targeting therapies such as sorafenib and radiation therapy (1-12).

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 (11,12). The survival benefit of TACE for unresectable HCC was established in two randomized controlled trials (RCTs) and in one meta-analysis (13-15). Thus, TACE plays an important role in treating unresectable HCC. It is clearly defined as a first-line therapy with an improved 2-year survival rate as compared with conservative therapy (16).

The Barcelona Clinic Liver Cancer (BCLC) classification is regarded as one of the most reliable staging and treatment strategy staging systems for HCC as it considers liver function, tumor status and performance status (PS) (16,17). The BCLC intermediate stage (BCLC-B) includes Child-Pugh A and B patients with multifocal HCC, defined as >3 tumors of any size or 2-3 tumors with a maximal diameter >3 cm and a single HCC (>5 cm) (24,36). To be categorized as intermediate-stage HCC, patients should be asymptomatic and have extrahepatic spread or no vascular invasion. The BCLC classification indicates that these patients are optimal candidates for TACE (16,17).

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In general, chemotherapeutic agents such as doxorubicin, epirubicin, cisplatin, mitomycin, 5-fluorouracil, zinostatin stimalamer and miriplatin are combined in TACE for the treatment of HCC; however, their treatment efficacy remains unclear (18). In cases where TACE was technically impossible due to anatomical reasons, a poor liver functional reserve or cessation of blood flow in the tumor feeding arteries recognized using lipiodol (iodine addition products of the ethyl esters of fatty acids obtained from poppy seed oil) chemolization alone, TACI was often performed in Japan. Indeed, Takayasu *et al* (11) reported in their large prospective Japanese nationwide study that out of 11,030 unresectable HCC patients who underwent transcatheter arterial therapies as an initial treatment, 2,523 patients (22.9%) were treated with TACI.

In our department, we have routinely performed TACE or TACI using an epirubicin-mitomycin-lipiodol (EML) emulsion for HCC when carrying out angiography (19,20). Epirubicin alone or in combination with other chemotherapeutic agents such as mitomycin has often been used in transcatheter arterial chemotherapy for HCC in Asian countries including Japan (18,21). However, to the best of our knowledge, whether TACE using an EML emulsion could benefit survival compared with TACI using an EML emulsion remains elusive. The aim of the present study was, therefore, to compare clinical outcomes between TACE and TACI, both using an EML emulsion, in patients with intermediate-stage HCC.

Materials and methods

Patients. We performed TACE therapy as an initial treatment in 148 treatment-naïve patients diagnosed with intermediate-stage HCC in the Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan, between January 2004 and December 2012. Of these patients, 145 were treated with TACE using an EML emulsion and 3 were treated with TACE using a miriplatin-lipiodol emulsion. During the same period, we performed TACI therapy as an initial treatment in 82 treatment-naïve patients diagnosed with intermediate-stage HCC in our department. Of these patients, 81 were treated with TACI using an EML emulsion and 1 patient was treated with TACI using a miriplatin-lipiodol emulsion. Thus, a total of 226 patients with intermediate-stage HCC [the TACE group (n=145) and the TACI group (n=81)] were analyzed in the present study. Patients diagnosed with HCC rupture at initial therapy were not included in the present study since they were treated with transcatheter arterial embolization without chemolization alone. We compared the overall survival (OS) and the treatment efficacy in the two groups.

Written informed consent was obtained from all patients prior to each therapy, and the study protocol complied with all the provisions of the Declaration of Helsinki. The present study was approved by the Ethics Committee of Osaka Red Cross Hospital, Japan, and the need for written informed consent in the present study was waived since 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 (16). Arterial- and portal-phase dynamic CT images were obtained at ~30 and 120 sec, respectively, after the injection of the contrast material. When carrying out angiography, we also confirmed intermediate-stage HCC using CT during hepatic arteriography (CTHA) and arterial-portography (CTAP) (22,23).

TACE and TACI procedures. In our angiography room, a catheter was advanced to the superior mesenteric artery and CTAP was performed to investigate the site and the size of the HCCs. Furthermore, we confirmed the patency of the portal vein at post-mesenteric portography. Then, a catheter was 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 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 targeted tumors. This was followed by an intra-arterial infusion via the feeding arteries according to tumor size and liver function of an emulsion containing epirubicin (Farmorubicin; Pfizer) at a mean dose of 39.7 ± 10.4 mg, mitomycin (Mitomycin C; Kyowa Hakko Kirin Company, Ltd., Tokyo, Japan) at a mean dose of 9.1 ± 3.2 mg and lipiodol at a mean dose of 5.7 ± 2.8 ml in the TACE group; in the TACI group, the emulsion contained epirubicin at a mean dose of 37.2 ± 9.9 mg, mitomycin at a mean dose of 9.0 ± 2.7 mg and lipiodol at a mean dose of 4.8 ± 1.9 ml (19,20,24). For patients treated with TACE after the infusion of an EML emulsion, gelatin sponge particles were injected slowly 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 dosages of the anticancer agents and lipiodol were reduced. The decision as to whether TACE or TACI was performed was mainly based on the recommendations of the attending physicians, who considered tumor-related factors, vascular anatomy and liver function. When selective catheterization of the tumor feeding arteries was technically impossible, TACI was performed. Additional embolization using gelatin sponge particles was not performed in patients when cessation of the blood flow in tumor feeding arteries was recognized using an infusion of an EML emulsion alone.

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 indicating necrosis. This was due to the fact that it had been previously reported in several studies that the lipiodol retention areas observed on CT corresponded to necrotic areas (25-27). Complete response (CR) was defined as the disappearance of all targeted tumors or 100% tumor necrosis, partial response (PR) was defined as a $\geq 50\%$ reduc-

Table I. Baseline characteristics between the TACE group and the TACI group.

Variables	TACE group (n=145)	TACI group (n=81)	P-value
Age (years)	72.5±9.1	70.3±9.3	0.083 ^a
Gender, male/female	94/51	57/24	0.462 ^b
Maximum tumor size (cm)	5.4±3.0	3.5±2.0	<0.001 ^a
Tumor number, >5/≤5	31/114	23/58	0.257 ^b
Tumor distribution, bilobar/unilobar	56/89	49/32	0.002 ^b
Child-Pugh classification, A/B	100/45	46/35	0.082 ^b
Causes of liver disease			
B/C/non B non C/B and C	12/93/39/1	7/56/18/0	0.843 ^b
Efficacy of initial treatment			
CR/PR/SD/PD	30/86/28/1	6/48/27/0	0.009 ^b
AST (IU/l)	61.8±32.5	67.9±48.0	0.260 ^a
ALT (IU/l)	48.9±34.3	54.7±48.5	0.294 ^a
ALP (IU/l)	417.3±221.0	430.6±183.0	0.646 ^a
GGT (IU/l)	140.1±202.1	120.8±138.4	0.446 ^a
Serum albumin (g/dl)	3.63±0.52	3.61±0.56	0.793 ^a
Total bilirubin (mg/dl)	1.07±0.85	1.19±0.73	0.273 ^a
Prothrombin time (%)	84.2±18.2	78.2±16.5	0.015 ^a
Platelets (x10 ⁴ /mm ³)	13.8±7.2	11.3±5.4	0.006 ^a
AFP (ng/ml)	1310.0±3693.9	3692.5±16082.5	0.192 ^a
DCP (mAU/ml)	9071.8±34906.2	5009.4±27603.3	0.339 ^a

Data are expressed as number or the mean ± standard deviation. TACE, transcatheter arterial chemoembolization; TACI, transcatheter arterial chemotherapy infusion; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ glutamyl transpeptidase; AFP, α -fetoprotein; DCP, des- γ -carboxy prothrombin; ^aunpaired t-test; ^bFisher's exact test.

tion 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 consisted of periodic blood tests and monitoring of tumor markers, including α -fetoprotein and des- γ -carboxy prothrombin (DCP). Dynamic CT scans and/or MRI were obtained every 2-4 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 therapies were performed if the liver functional reserve was adequate and if patients did not refuse such therapies. They 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, molecular targeting therapy such as sorafenib was also considered.

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 mortality 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 <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 indicate statistically significant differences.

Results

Baseline characteristics. The baseline characteristics of the patients in the two groups are shown in Table I. The median observation period was 1.8 years (range, 0.2-9.0 years) in the TACE group and 2.0 years (range, 0.2-8.7 years) in the TACI group. The mean age in the TACE group (72.5±9.1 years) tended to be higher (P=0.083) than that in the TACI group (70.3±9.3 years). Maximum tumor diameter was significantly larger (P<0.001) in the TACE group (5.4±3.0 cm) than in the TACI group (3.5±2.0 cm). The proportion of patients with

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	151/75	0.415		
Age (years), >70 vs. ≤70	123/103	0.113		
TACE vs. TACI	145/81	0.691		
Child-Pugh, A vs. B	146/80	<0.001	0.526 (0.310-0.892)	0.017
Tumor number, >5 vs. ≤5	54/172	0.011	0.631 (0.403-0.989)	0.045
Tumor distribution, bilobar vs. unilobar	105/121	0.003	1.125 (0.736-1.721)	0.586
Maximum tumor size, >4 cm vs. ≤4 cm	106/120	0.005	0.864 (0.583-1.279)	0.465
Objective response at initial therapy, yes/no	170/56	0.165		
AST (IU/l), >50 vs. ≤50	122/104	0.648		
ALT (IU/l), >40 vs. ≤40	116/110	0.158		
ALP (IU/l), >380 vs. ≤380	106/120	0.077		
GGT (IU/l), >80 vs. ≤80	101/125	0.381		
Serum albumin level (g/dl), ≥3.7 vs. <3.7	113/113	0.001	1.260 (0.795-1.996)	0.325
Total bilirubin (mg/dl), ≥1.0 vs. <1.0	101/125	0.023	0.888 (0.603-1.307)	0.546
Platelet count (×10 ⁴ /mm ³), >12 vs. ≤12	110/116	0.651		
Prothrombin time (%), >80 vs. ≤80	125/101	0.044	0.935 (0.593-1.475)	0.772
Serum AFP (ng/ml), >100 vs. ≤100	80/146	0.053		
DCP (mAU/ml), >100 vs. ≤100	156/70	<0.001	0.483 (0.304-0.765)	0.002

CI, confidence interval; TACE, transcatheter arterial chemoembolization; TACI, transcatheter arterial chemotherapy infusion; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ glutamyl transpeptidase; AFP, α -fetoprotein; DCP, des- γ -carboxy prothrombin; ^aCox proportional hazard model.

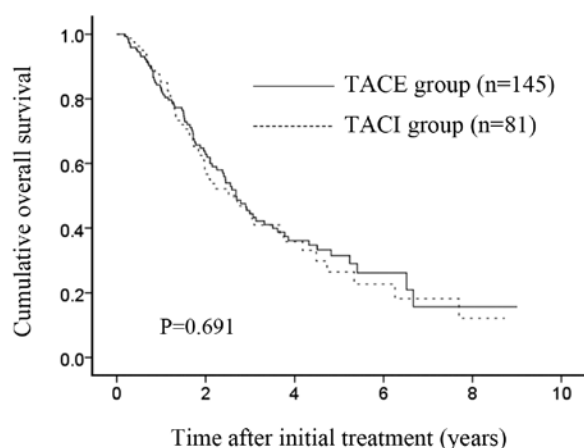


Figure 1. Median survival time (MST) and cumulative overall survival (OS) for patients in the TACE and TACI groups. The MST was 2.68 years in the TACE group and 2.64 years in the TACI group. The 1-, 2-, 3- and 5-year cumulative OS rates were 81.5, 63.4, 43.9 and 32.7%, respectively, in the TACE group, and 85.0, 60.0, 43.2 and 26.0%, respectively, in the TACI group (P=0.691).

bilobar disease was significantly lower (P=0.002) in the TACE group than in the TACI group. The prothrombin time (PT) and platelet count were significantly higher in the TACE group than in the TACI group. The proportion of patients with Child-Pugh class A disease was significantly higher in the TACE group than in the TACI group. These findings indicated that

patients in the TACE group had a superior liver functional reserve to those in the TACI group.

Median survival time and cumulative OS rates. The median survival time (MST) and the 1-, 2-, 3- and 5-year cumulative OS rates were 2.68 years and 81.5, 63.4, 43.9 and 32.7%, respectively in the TACE group, and 2.64 years and 85.0, 60.0, 43.2 and 26.0%, respectively in the TACI group; there was no significant difference (P=0.691) in these parameters between the two groups (Fig. 1).

Treatment efficacy at initial treatment in the two groups. In the TACE group, a CR was achieved in 30 patients, a PR in 86 patients, SD in 28 patients and PD in one patient. Thus, the objective response rate (ORR) in the TACE group was 80.0% (116/145 patients). In the TACI group, a CR was achieved in 6 patients, a PR in 48 patients, SD in 27 patients; no patient had PD. Thus, the ORR in the TACI group was 66.7% (54/81 patients). In terms of treatment efficacy, the TACE group achieved significantly improved treatment efficacy relative to the TACI group (P=0.009).

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=226): the Child-Pugh classification (P<0.001); tumor number ≤5 (P=0.011); tumor distribution (P=0.003); a maximum tumor size

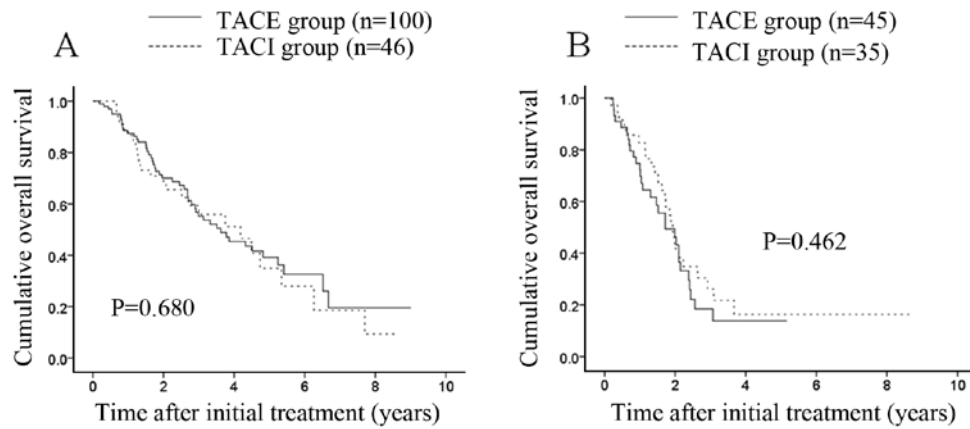


Figure 2. Subgroup analysis according to Child-Pugh classification. (A) There were 100 patients with Child-Pugh class A disease in the TACE group and 46 in the TACI group. The MST was 3.62 years for patients in the TACE group and 4.18 years for patients in the TACI group. The difference in the two groups did not reach significance in terms of OS ($P=0.680$). (B) There were 45 patients with Child-Pugh class B disease in the TACE group and 35 in the TACI group. The MST was 1.72 years for patients in the TACE group and 1.93 years for patients in the TACI group. The difference in the two groups did not reach significance in terms of OS ($P=0.462$).

≤ 4 cm ($P=0.005$); a serum albumin level ≥ 3.7 g/dl ($P=0.001$); a total bilirubin level ≥ 1.0 mg/dl, a PT $>80\%$ ($P=0.044$) and a DCP >100 mAU/ml ($P<0.001$) (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 ($P=0.017$); tumor number ≤ 5 ($P=0.045$) and DCP >100 mAU/ml ($P=0.002$) were found to be significant predictors linked to OS in multivariate analysis.

Causes of mortality. Seventy-nine patients in the TACE group (54.5%) died during the follow-up period. The causes of mortality were HCC progression in 48 patients, liver failure in 23 patients and miscellaneous causes in 8 patients. Fifty patients in the TACI group (61.7%) died during the follow-up period and the causes of mortality were HCC progression in 28 patients, liver failure in 15 patients and miscellaneous causes in 7 patients.

Adverse events in the two groups. In both groups, symptoms associated with postembolization syndrome such as fever, appetite loss, abdominal pain and nausea were transient and were mostly resolved within 2 weeks after initial treatment (28). In the TACE group, serious adverse events (SAEs) were observed in 8 patients (5.5%). These 8 patients had one of the following SAEs: acute respiratory distress syndrome (ARDS), hepatic encephalopathy, cholangitis, hyponatremia, hyperbilirubinemia, aspiration pneumonia, liver abscess and refractory ascites. All SAEs were managed successfully, although in 1 patient who developed ARDS, management in the intensive care unit was required. Thus, TACE-related mortality was 0%. In the TACI group, SAEs were observed in 2 patients (2.5%) and included gastrointestinal bleeding and liver abscess in 1 patient each. These SAEs were successfully managed and TACI-related mortality was also 0%.

Subgroup analysis according to the Child-Pugh classification. Marginal significance was observed between the two groups in terms of the Child-Pugh classification ($P=0.082$), and we, therefore, performed subgroup analyses according

to this classification. No significant difference ($P=0.680$) was observed between the two groups in terms of OS in patients with Child-Pugh class A disease [100 patients (69.0%) in the TACE group and 45 patients (55.6%) in the TACI group]; the MST was 3.62 years in the TACE group and 4.18 years in the TACI group (Fig. 2A). Similarly, no significant difference ($P=0.462$) was found between the two groups in terms of OS in patients with Child-Pugh class B disease [45 patients (31.0%) in the TACE group and 36 (44.4%) in the TACI group]; the MST was 1.72 years in the TACE group and 1.93 years in the TACI group (Fig. 2B).

Subgroup analysis according to maximum tumor size. The maximum tumor size was significantly larger in the TACE group than in the TACI group ($P<0.001$). Consequently, we performed subgroup analyses according to maximum tumor size. No significant difference ($P=0.801$) was observed between the two groups in terms of OS in patients with a maximum tumor size >4 cm [82 patients (56.6%) in the TACE group and 24 (29.6%) in the TACI group]; the MST was 2.15 years in the TACE group and 1.93 years in the TACI group (Fig. 3A). Similarly, no significant difference was found between the two groups in terms of OS ($P=0.269$) in patients with a maximum tumor size ≤ 4 cm [63 patients (43.4%) in the TACE group and 57 (70.4%) in the TACI group]; the MST was 3.51 years in the TACE group and 2.92 years in the TACI group (Fig. 2B).

Subgroup analysis according to tumor distribution. The proportion of patients with bilobar disease was significantly lower in the TACE group than in the TACI group ($P=0.002$). Hence, we performed subgroup analysis in terms of tumor distribution. There were 56 (38.6%) patients with bilobar disease in the TACE group and 49 (60.5%) in the TACI group. In terms of OS, there was no significant difference ($P=0.289$) between the two groups; the MST was 2.25 years in the TACE group and 2.23 years in the TACI group (Fig. 4A). There were 89 (61.4%) patients with unilobar disease in the TACE group and 32 (39.5%) in the TACI group. In terms of OS, there was no significant difference ($P=0.564$) between the two groups; the MST was 3.51 years in the TACE group and 3.09 years in the TACI group (Fig. 4B).

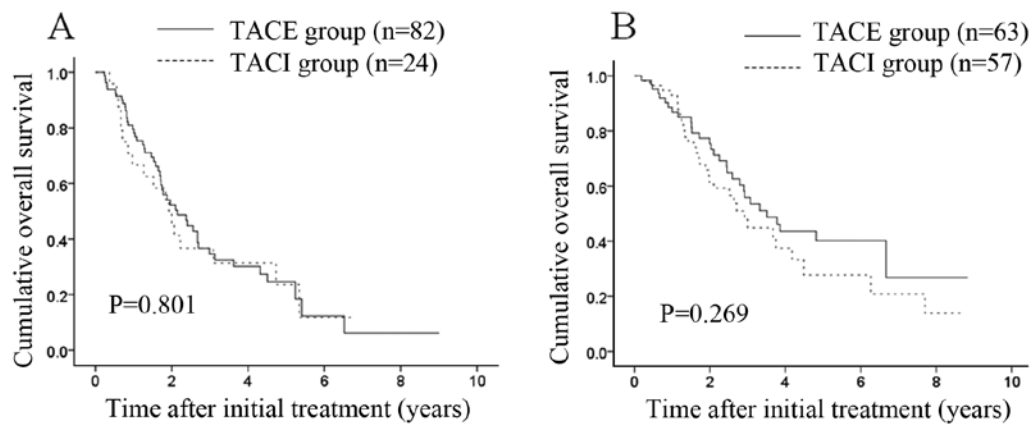


Figure 3. Subgroup analysis according to maximum tumor size. (A) There were 82 patients with a maximum tumor size >4 cm in the TACE group and 24 in the TACI group. The MST was 2.15 years for patients in the TACE group and 1.93 years for patients in the TACI group. There was no significant difference ($P=0.801$) between the two groups in terms of overall survival (OS). (B) There were 63 patients with maximum tumor size ≤ 4 cm in the TACE group and 57 in the TACI group. The MST was 3.51 years for patients in the TACE group and 2.92 years for patients in the TACI group. There was no significant difference in the two groups in terms of OS ($P=0.269$).

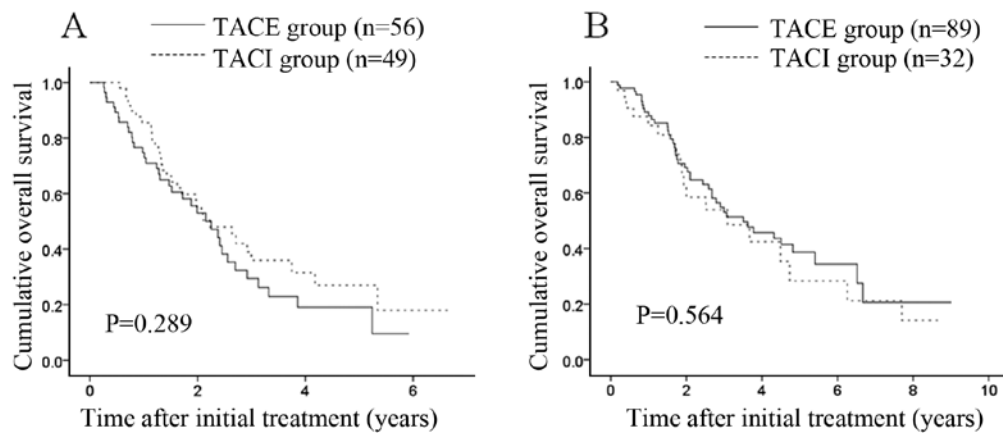


Figure 4. Subgroup analysis according to tumor distribution. (A) There were 56 patients with bilobar disease in the TACE group and 49 in the TACI group. The MST was 2.25 years for patients in the TACE group and 2.23 years for patients in the TACI group. No significant difference ($P=0.289$) was observed in the two groups in terms of overall survival (OS). (B) There were 89 patients with unilobar disease in the TACE group and 32 in the TACI group. The MST was 3.51 years for patients in the TACE group and 3.09 years for patients in the TACI group. No significant difference was observed between the two groups in terms of OS ($P=0.564$).

Discussion

Okusaka *et al* (29) conducted an RCT that compared clinical outcomes between unresectable HCC patients treated with TACE using zinostatin stimalamer ($n=79$) and those treated with TACI using zinostatin stimalamer ($n=82$). They concluded that treatment intensification involving the addition of embolization did not improve survival over TACI with zinostatin stimalamer. Similarly, Ikeda *et al* (30) carried out a retrospective comparative study regarding clinical outcomes between HCC patients treated with TACE using cisplatin suspended in lipiodol ($n=74$) and patients treated with TACI using cisplatin suspended in lipiodol ($n=94$). They reported that TACE using cisplatin suspended in lipiodol had a higher treatment efficacy than TACI using cisplatin suspended in lipiodol, but that it did not significantly improve the survival of patients with HCC. However, it remains unclear as to whether or not TACE using an EML emulsion can deliver a survival benefit over TACI using an EML emulsion; hence the reason for the present compara-

tive study. To the best of our knowledge, this is the first study to compare clinical outcomes in intermediate-stage HCC patients using TACE and TACI, both with an EML emulsion.

In the present study, the MST was 2.68 years for patients in the TACE group and 2.64 years for patients in the TACI group. Takayasu *et al* (12) reported that the MST was 2.83 years in 8510 HCC patients who underwent TACE. Our findings were similar to theirs, although their study population analysis included patients with early-, intermediate- and advanced-stage HCC (12). Here, in all cases and in all subgroup analyses, the difference between the TACE and the TACI group did not reach statistical significance in terms of OS. Our results suggest that TACI using an EML emulsion could achieve a comparable survival benefit to TACE using an EML emulsion, although the treatment efficacy after initial therapy in the TACE group was significantly higher than that in the TACI group. Intermediate-stage HCC includes heterogeneous patient populations with varying tumor size, tumor distribution, tumor number and liver function (31). Thus, all patients with intermediate-stage

HCC might not derive a similar survival benefit from TACE. In fact, in patients with Child-Pugh class B disease, the MST in the TACI group was longer than that in the TACE group in the present study. In patients where TACE was technically impossible for anatomical reasons, or in patients with poor liver function whose liver function was expected to deteriorate if TACE was performed, TACI using an EML emulsion was an acceptable alternative.

Epirubicin and doxorubicin are anthracycline-based anticancer drugs (18). Both drugs have been conventionally used in TACE or TACI for the treatment of patients with HCC (18). Since epirubicin can easily undergo glucuronidation, it is less toxic than doxorubicin (18). Furthermore, TACE or TACI using cisplatin may cause renal dysfunction or a hypersensitivity reaction, and TACE or TACI using zinostatin stimalamer causes severe vascular endothelial damage and loss of the hepatic artery for infusion (18,32). This is the reason why we have routinely used an epirubicin containing regimen in transcatheter arterial chemotherapy for HCC.

In our multivariate analysis, Child-Pugh classification, tumor number and DCP value were revealed as being significant predictors linked to OS. As mentioned earlier, Takayasu *et al* (12) conducted a large nationwide prospective cohort study in 8,610 HCC patients treated with TACE. Their multivariate analysis revealed that the degree of liver damage, tumor marker, maximum tumor size, tumor number and portal vein invasion were significantly associated with OS (12); our results were consistent with those reported in that study. Preserving liver function in HCC patients treated with transcatheter arterial therapies may be one of the key factors for optimizing clinical outcome (33). However, it is of interest that objective tumor response after initial therapy was not a significant predictor linked to OS in the present study. Even if treatment response after initial therapy was poor, performance of the most appropriate therapy at disease progression may be associated with favorable clinical outcomes.

In the present study, molecular targeted therapies were performed (sorafenib was approved for its use in 2009 in Japan) in 14 patients (9.7%) in the TACE group and in 3 patients (3.7%) in the TACI group. In practice, the point at which transcatheter arterial therapies should be replaced by targeted molecular therapy in patients with HCC refractory to transcatheter arterial therapies is a critical issue (34). We did not examine this issue in the present study; future studies will therefore be required.

In this study, TACE or TACI-related mortality was 0% in both groups. TACE-related mortality has been reported to range from 0.5 to 7% (12,35,36). Relative to these other studies, our transcatheter arterial therapy procedure was safe.

The present study had several limitations. First, it was a retrospective study. Second, the choice of TACE or TACI in the treatment of HCC was mainly based on the decision of the attending physicians, leading to bias. Third, patient characteristics in the two groups were not well balanced for analysis, also leading to bias. Future prospective studies with well-balanced cohorts are, therefore, required to overcome these limitations. However, our results demonstrated that patients in the TACI group had a similar prognosis to patients in the TACE group. In conclusion, TACI using an EML emulsion can be considered as one of the therapeutic options for the treatment of intermediate-stage HCC.

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