Original Article

Efficacy and Safety of Transarterial Chemoembolization in Patients with Intermediate and Advanced Stages of Hepatocellular Carcinoma

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ABSTRACT

Background: Transarterial chemoembolization (TACE) is the standard of care for patients with intermediate stage hepatocellular carcinoma (HCC). However, due to limited accessibility for targeted therapy, TACE is sometimes utilized in patients with more advanced stages of HCC, including those with portal vein thrombosis/invasion (PVT) and extra-hepatic metastases. Safety and efficacy data of TACE in these settings are limited.

Objective: To determine the efficacy and safety of TACE in patients with intermediate and advanced stages of HCC according to Barcelona Clinic Liver Cancer (BCLC) staging system.

Methods: Data of consecutive patients with intermediate or advanced HCC who underwent TACE between January 2008 and December 2012 in a single tertiary center (Rajavithi Hospital, Bangkok) were retrospectively reviewed. TACE was performed under the standard hospital protocol by 3 experienced radio-interventionists. HCC patients with BCLC-B were classified as "standard TACE criteria" group, whereas patients with BCLC-C were classified as "extended TACE criteria" group. The primary endpoint was an overall 2-year survival. Secondary endpoints were safety and objective tumor response to TACE.

Results: A total of 110 HCC patients who underwent TACE were included in the analysis. There was no significant difference in the overall survival between the standard criteria group (n=56) and the extended criteria group (n=54): 2-year survival 15.2% vs 14.3%, p=0.555; median survival, 9.6 vs 7.7 months; p=0.535, respectively. Progressive disease by modified RECIST criteria was more common in the extended criteria group (10.7% vs 31.5%, p=0.007). Pre-treatment MELD score, PVT and TACE-related complications were independent factors for survival in a multivariate analysis. The median survival of patients with and without PVT was 5.6 and 11.2 months (p<0.001), respectively. There was no difference in survival between patients with and without extra-hepatic metastases (9.6 vs 8.5 months, p=0.784). The incidence of TACE-related complications were similar between the two groups (p<0.05): 32.1% liver decompensation and 3.6% death in the standard criteria group; and 35.2% liver decompensation and 5.6% death in the extended criteria group.

Conclusion: The overall median survival and adverse events following TACE were similar between HCC patients with BCLC stage B and stage C. This finding supports the use of TACE to slow down HCC progression in selected patients with BCLC-C, including those with extra-hepatic metastasis.

Key words : Transarterial chemoembolization, TACE, hepatocellular carcinoma, HCC

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Introduction

Hepatocellular carcinoma (HCC) is a major cause of liver related morbidity and mortality. HCC is the seventh most common cancer and the third leading cause of cancer-related death worldwide[1]. Curative therapies including surgical resection, liver transplantation and percutaneous ablation are now a standard treatment option for patients with early-stage HCC[2-4]. Unfortunately, the majority of HCC patients especially in developing countries including Thailand, were diagnosed at advanced stages[5]. These patients are not eligible for potentially curative therapy because of poor liver function[6,7].

Transarterial chemoembolization (TACE) is the most appropriate palliative treatment for patients who have progressed beyond an early stage, as symptoms are usually absent at this stage[8-10]. Surveillance programs for liver cancer among high-risk groups have not been widely conducted in Thailand. Such patients these have limited access for treatment, poor prognosis and high mortality rate[11,12].

According to the Barcelona Clinic Liver Cancer Staging (BCLC Staging) treatment guideline, patients with BCLC advanced-stage (stage C) disease were defined by an Eastern Cooperative Oncology Group (ECOG) performance status of 1-2, and/or portal vein branch invasion, and/or extra-hepatic metastases. Previous studies showed that portal vein thrombosis (PVT) and extra-hepatic metastasis were the most important prognostic factors affecting survival in unresectable HCC patients who underwent TACE[13], as the procedure increased the risk of hepatic insufficiency. Patients with BCLC stage C should receive palliative systemic chemotherapy with sorafenib -multikinase inhibitor[13]. However, a case study by Takahide Nakazawa, *et al*., demonstrated that the low median survival was 4.5 months in advanced stage HCC patients treated with sorafenib[14-16]. Two randomized control trials confirmed that patients with HCC who received TACE were better off in term of survival as compared with conservative treatment. Moreover TACE was safe in selected patients[17,18].

In the present retrospective study, we aimed at determining and analyzing the survival benefit of TACE treatment in patients with unresectable HCC and with vascular invasion and/or extra-hepatic metastasis.

Patient and methods

Study design and patients selection

The present study was a single center retrospective analysis conducted between January 2008 and December 2012. The diagnosis of HCC was is accordance with the American Association Study of Liver Disease (AASLD) criteria. All patients were treated with TACE.

Inclusion criteria were age over 18 and diagnosed advanced HCC (BCLC stage C) with TACE treatment. Subjects were excluded if they (a) had undergone surgery, percutaneous ablation or radiation therapy before or after TACE, (b) were Child-Pugh class C liver disease, (c) had vascular invasion, namely involvement of the portal vein, the hepatic vein, the inferior vena cava (IVC) or their branches as identified by imaging techniques showing presence of tumor thrombus or partial occlusion of the main branches of the portal vein or the IVC.

The diagnosis of HCC was based on criteria as stated in the AASLD guideline, which included an persistently elevated serum alpha-fetoprotein level (>200 ng/mL) and typical features on computed tomography (CT) or magnetic resonance imaging (MRI) consistent with the diagnosis of HCC. For patients who did not meet the clinical criteria, liver biopsy was performed to confirm the HCC diagnosis. TACE was offered as palliative treatment for all patients.

During the 5-year study period, there were 671 HCC patients undergoing TACE at Rajavithi Hospital. One-hundred-and-ten HCC patients were available for complete medical record reviews. Patients' profile including general information laboratory investigation results, baseline liver function tests, renal function tests, coagulogram, complete blood count, AFP level, sizes of tumors from diagnostic radiology investigations, evidence of portal vein and IVC invasion by tumors, and extra-hepatic metastases. Serious complications or adverse events associated with post-TACE treatments, survival after the first TACE, and causes of death were collected.

Procedure and technique

TACE was performed under sterile technique with local anesthesia and fluoroscopic guidance in accordance with the hospital protocol. Chemoembolization was carried out as selectively as possible via the lobar, segmental, or subsegmental arteries, depending on tu-

mor distribution and patient's hepatic functional reserve. Amoxycillin/clavulanate (Augmentin®) 1.2 gram was chosen as a prophylactic antibiotic. The right common femoral artery was punctured and replaced with a 5-French sheath. Visceral angiogram was them performed in the celiac and the superior mesenteric arteries using a 5-French Simmon-1 catheter. When the location of the feeding vessel of the tumor was identified, Lipiodol 10 milliliters mixed with Mitomycin-C 20 milligrams was injected into the vessel. Pieces of gelfoam were subsequently injected to embolize the artery.

Follow up

CT scan and serum AFP were taken within 4-6 weeks after TACE to assess tumor response. The next TACE was scheduled 6-8 weeks after the previous TACE. Patients who had residual viable tumor or recurrent tumor on CT/MRI underwent a repeated TACE if they were Child-Pugh class A or B without evidence of hepatic decompensation (such as high level of bilirubin, uncontrolled ascites, or hepatic encephalopathy).

The primary endpoints of the study were the overall survival (OS) and the 2-year survival. Secondary endpoints were safety and efficacy of TACE therapy in advanced HCC.

Statistical analyses

All statistical analyses were performed by using SPSS version 17.0. To determine significant differences between the two groups, the continuity correction and independent-samples *t*, Pearson x^2, and Fisher exact tests were used. Survival curves were calculated for both groups by using Kaplan-Meier methods. Univariate analyses were performed with the log-rank test. Variables with a *p*-value of less than 0.05 at univariate analysis were entered into a multivariate analysis. Multivariate analyses were performed with a Cox proportional hazard regression model. Wilcoxon signed-rank test was used to determine the difference in liver function test values before and after treatment. All statistical tests were two-tailed, and $p< 0.05$ indicated a significant difference.

RESULTS

A total of 110 consecutive patients who fulfilled the criteria of the study protocol were enrolled and their medical records reviewed. The reasons for tumor unresectability were bilobar involvement, major vessel involvement, and extra-hepatic metastases. Surgery was contraindicated in our entire patient. Six-hundred-and-seventy-one patients were excluded due to incomplete data (n = 243), prior surgery (n = 172), BCLC stage A (n = 92), prior RFA (n = 46), prior bridging therapy (n = 2), and concomitant non-hepatic malignancy (n = 6).That were classified as 56 (50.9%) and 54 (49.1%) of BCLC stage B (control group) and C (exceptional criteria group) respectively.

The baseline characteristics of the patients and of the tumors are shown in Table 1 and 3.There were 45 males (80.4%) in the control group and 45(83.3%) in the study group, with a mean age of 54.04 ± 11.09 years and 58.29 ± 11.09 respectively. Hepatitis B virus (HBV) infection was the most common etiologic factor of HCC [58 (51.6%) patients]. Alcohol was the second most common etiologic factor [40 (36.4%) patients]. Other etiologies were recorded in 26 (23.6%) of patients.

The laboratory characteristics were not significantly different in both groups. The mean and the standard deviation were as follow: Hb 11.63±1.92 g/dL, ANC 5,097 u/L, platelet 245,945.65 u/L, GFR 80.25±28.92 mL/min/1.73 m^2, total billirubin 1.15±0.8 mg/dL, AST 128.82±119.7 U/L, ALT 64.26±63.62 U/L, and albumin 3.53±0.51 g/dL. The mean±SD of each group are shown in Table 2.

The baseline characteristics regarding TACE were not significantly different in the BCLC-B group and the BCLC-C group. In the study group, extra-hepatic metastases were seen in 31 (57.4%), vascular invasion in 50 (92.6%), partial in evolvement of the main portal vein in 5 (9.3%), in vision of portal vein branches in 35 (64.8%), and IVC invasion in 10 (18.5%). CTP class A was noted in 45 cases (80.4%) and 40 cases (74.1%) respectively. Tumor size greater than or equal to 5 cm. was seen in 48 patients (85.7%) in the control group and 50 (92.6%) in the study group.

The mean follow-up duration was 11.3 months (range, 1-24 months). The median overall survival was 8.79 (95% CI: 7.33, 10.25 months). The median time survival time in the BCLC-B group was 9.57 months (95% CI: 6.49, 12.66 months), and in the BCLC-C groups was 7.74 months (95% CI: 5.73, 9.75 months), no significant difference ($p= 0.535$). The median survival time for patients with portal vein invasion was 5.61 months (95% CI: 3.88, 7.75 months), and 9.57 months for those with extra-hepatic metastasis (95%

Table 1. Baseline patient characteristics.

Characteristics	Control (n=56)	Study (n=54)	*p*-value
Male	45 (80.4%)	45 (83.3%)	0.686
Age (year)	58±11	54±11	0.047
<50, n (%)	10 (17.9%)	18 (33.3%)	0.063
≥50, n (%)	46 (82.1%)	36 (66.7%)	0.063
Alcohol (concurrent), n (%)	31 (55.4%)	39 (72.2%)	0.066
Smoking, n (%)	19 (33.9%)	32 (59.3%)	0.008
Etiology, n (%)			
CHB	30 (53.6%)	28 (51.9%)	0.857
CHC	12 (21.4%)	14 (25.9%)	0.579
Alcohol	19 (33.9%)	21 (38.9%)	0.589
HT, n (%)	20 (35.7%)	7 (13%)	0.006
BMI (kg/m^2)	21.13±3.1	20.88±3.3	0.677
CTP Class			
A	45 (80.4%)	40 (74.1%)	0.432
B	11 (19.6%)	14 (25.9%)	0.432
MELD score			
mean (range)	9 (8, 10)	9 (8, 11)	0.400
<15, n (%)	54 (96.4%)	51 (94.4%)	0.618
≥15, n (%)	2 (3.6%)	3 (5.6%)	0.618

*Control= standard criteria group, Study= extended criteria group

Table 2. Baseline laboratory characteristics.

Characteristics	Control (n=56)	Study (n=54)	*p*-value
AFP (mg/dL)	9,719.34±16,735.06	13,806.07±20,974.04	0.238
TB (mg/dL)	1.09±0.83	1.23±0.74	0.369
AST (U/L)	115.91±115.78	142.57±120.77	0.021
ALT (U/L)	66.48±74.90	64.63±50.08	0.291
Albumin (g/dL)	3.54±0.55	3.53±0.47	0.965
INR	3.54±0.55	3.53±0.47	0.618
GFR(mL/min/1.73 m^2)	73.18±24.66	87.59±31.33	0.008

*Control= standard criteria group, Study= extended criteria group

CI: 4.27, 14.88 months). The 1-year and 2-year median survival rates were 44.6% (95%CI: 31.4-57), 14.3% (95%CI: 6.2-25.7) and 38.9% (95%CI: 26-51), 15.2% (95%CI: 7-26.5).

TACE-related adverse events occurring within 2 weeks post-treatment are shown in Table 5. Post-TACE syndrome was most commonly noted in both groups without significant difference. Additionally, 17 (30.4%) of 56 patients in the BCLC-B group and 16 (29.6%) of the 54 patients in the BCLC-C group had procedure-related complications, including liver decompensation, GI bleeding and acute liver failure. Five (4.55%) patients died, 4 from acute liver failure and 1 from pneumonia with sepsis.

Adverse events occurred in 47 (83.9%) of 56 patients in the BCLC-B group, and 43 (79.6%) of 54 patients in the BCLC-C group. The occurrence rates of adverse events between the two groups were not sig-

Table 3. Baseline tumor characteristics.

Characteristics	Control (n=56)	Study (n=54)	*p*-value
Tumor number, n (%)			0.605
Single	16 (286%)	13 (24.1%)	
2-3	11 (19.6%)	8 (14.8%)	
>3	29 (51.8%)	33 (61.1%)	
Size, n (%)			
<5 cm	8 (14.3%)	4 (7.4%)	0.247
≥5 cm	48 (85.7%)	50 (92.6%)	0.247
Portal vein invasion, n (%)	0 (0%)	40 (74.1%)	0.001*
Portal position, n (%)			
Left or Right	0 (0%)	35 (64.8%)	NA
Main	0 (0%)	5 (9.3%)	NA
IVC, n (%)	0 (0%)	10 (18.5%)	NA
Metastasis, n (%)	0 (0%)	31 (57.4%)	NA
Lymph node	0 (0%)	18 (33.3%)	NA
Lung	0 (0%)	7 (13%)	NA
Bone	0 (0%)	6 (11.1%)	NA
Adrenal gland	0 (0%)	3 (5.6%)	NA

*Control= standard criteria group, Study= extended criteria group

Table 4. TACE results.

Characteristics	Control (n=56)	Study (n=54)	*p*-value
No. TACE, n (range)	2 (1, 3)	2 (1, 3)	0.762
Tumor response, n (%)			
Complete response (CR)	3 (5.4%)	4 (7.4%)	0.660
Partial response (PR)	32 (57.1%)	10 (18.5%)	0.001
Stable disease (SD)	13 (23.2%)	18 (33.3%)	0.238
Progressive disease (PD)	6 (10.7%)	17 (31.5%)	0.007
Objective response	35 (62.5%)	14 (25.9%)	0.001
Non-response	19 (33.9%)	35 (64.8%)	0.001
Disease control	48 (85.7%)	32 (59.3%)	0.002

Objective response = CR+PR, Non-response = SD+PD, Disease control = CR+PR+SD

Table 5. Adverse events related to TACE.

Adverse Event	Control (n=56)	Study (n=54)	*p*-value
Post TACE syndrome	47 (83.9%)	43 (79.6%)	0.559
AKI	5 (8.9%)	5 (9.3%)	0.952
Abscess	1 (1.8%)	0 (0%)	0.324
GI bleeding	2 (3.6%)	5 (9.3%)	0.222
Liver decompensated	17 (30.4%)	16 (29.6%)	0.934
Liver failure	1 (1.8%)	3 (5.6%)	0.291
Death	2 (3.6%)	3 (5.6%)	0.618

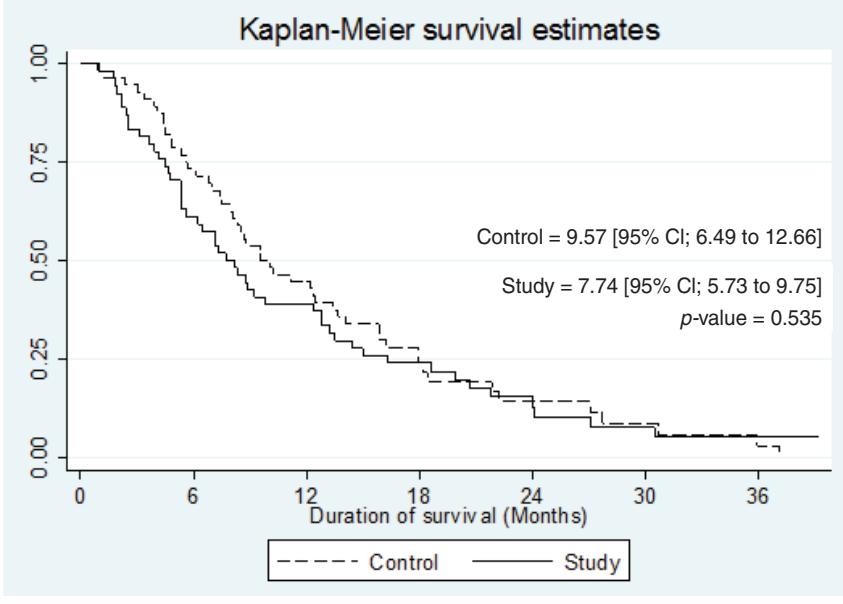

Figure 1. Kaplan-Meier Survival curve by group.

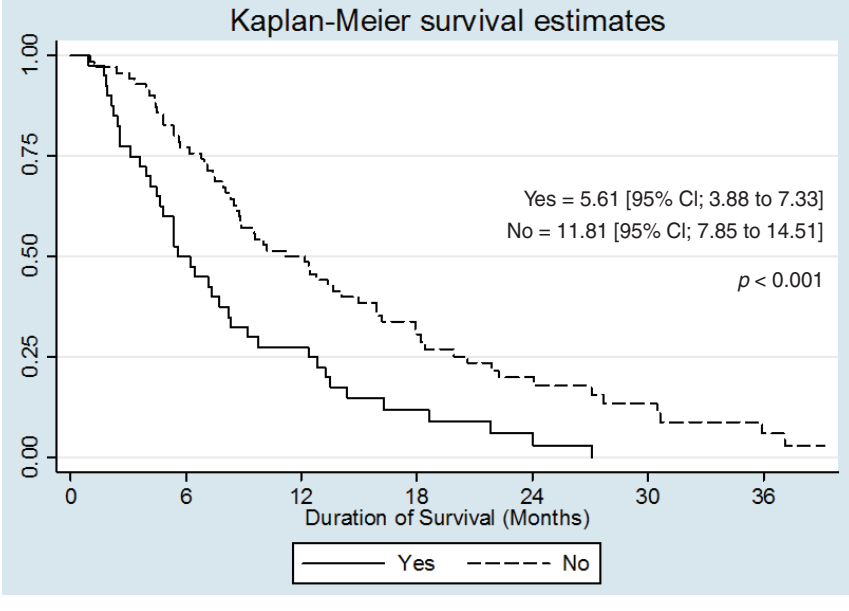

Figure 2. Kaplan-Meier Survival curve by portal vein invasion.

nificantly different. Liver function at 2 weeks post TACE showed irreversible worsening in 17 (30.4%) and in 16 (29.6%) of patients in the two groups respectively.

Discussion

According to recent AASLD guideline, patients with advanced HCC should be treated with sorafenib. However, in Asia and Africa, where over 80% of global HCCs occur, there are considerable variation in terms of etiology and staging of HCC at the time of diagnosis[2]. Curative surgery is a therapeutic option in only 15% of HCC cases, owing to large tumor size, multiplicity of the primary tumors, or the accompanying cirrhosis. Palliative TACE has been widely chosen to treat HCC in patients who are not candidates for surgery[3,15]. Most advanced HCC patients in Thailand

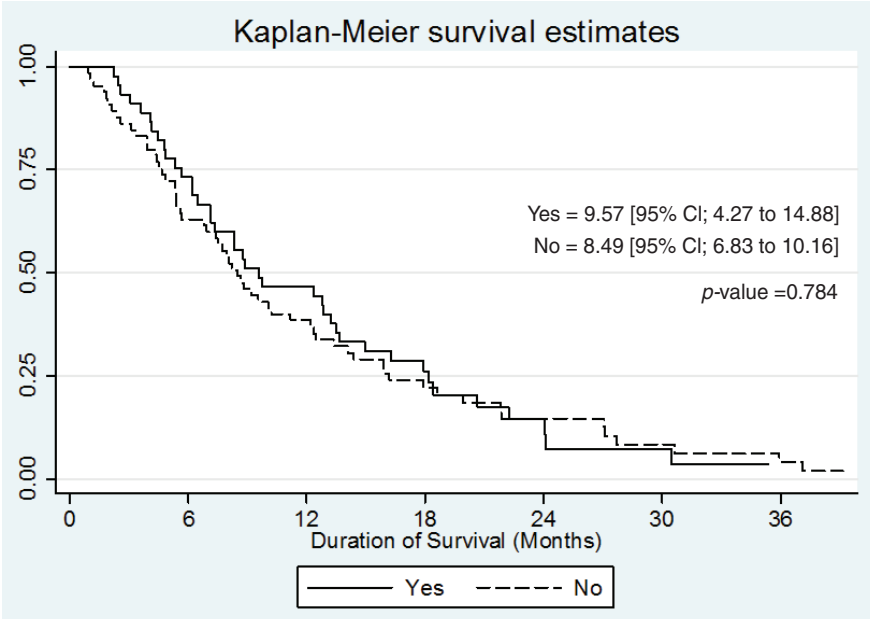

Figure 3. Kaplan-Meier Survival curve by metastasis.

Table 6. Univariate analysis of prognostic factors for OS.

Factors	HR (95%CI for HR)	*p*-value
Study group	1.13 (0.76, 1.68)	0.536
Age (year)	0.97 (0.95, 0.99)	0.003
Male	1.86 (1.1, 3.14)	0.020
Alcohol (concurrent)	1.46 (0.96, 2.22)	0.076
Portal vein invasion	2.11 (1.39, 3.19)	0.001
Portal position (Left or Right)	0.36 (0.13, 0.99)	0.047
IVC	0.75 (0.37, 1.51)	0.420
Metastasis	0.95 (0.63, 1.42)	0.784
CTP score	1.27 (1, 1.61)	0.051
MELD score	1.14 (1.06, 1.23)	0.001
Albumin score	1.1 (0.8, 1.52)	0.568
Size >5 cm	1.45 (0.77, 2.72)	0.248
Progressive disease	2.51 (1.56, 4.06)	0.001
Stable or Progressive disease	1.78 (1.18, 2.69)	0.006
Procedure-related complications	2.45 (1.57, 3.84)	<0.001

Table 7. Multivariate analysis of prognostic factors for OS

Factors	HR (95%CI for HR)	*p*-value
Procedure-related complications	1.95 (1.21, 3.15)	0.006
Portal vein invasion	3.37 (1.63, 6.98)	0.001
MELD score	1.1 (1.02, 1.19)	0.018

(BCLC-B and BCLC-C) are from the low socioeconomic sector with low income, who cannot afford the recommended standard treatment by Barcelona staging criteria[5]. At Rajavithi Hospital, Bangkok, BCLC stage C patients who should receive systemic chemotherapy (Sorafenib) are frequently offered TACE instead, for financial reason. We, therefore, wanted to compare treatment efficacy, safety and survival between the group receiving TACE by the Barcelona staging criteria and the group under exceptional criteria.

In our study, we found that the 1-year and the 2-year median survival times were not different between the two groups (Figure 4). In a previous study, the overall median survival of 5.2 months and the 12-month and 24-month overall survival rates of 18.3% and 5.6% respectively were reported[10].Our study noted an overall median survival of 8.79 months while the 12-month and the 24-month overall survival rates were 38.9% and 15.2% in the exceptional criteria group. Our results suggested that an exceptional criteria TACE treatment may be considered another optional treatment for the advanced HCC patients.

We found also that after treatment, the rate of tumor progression was higher in the exceptional criteria group than in the standard BCLC criteria group (Table 3). However, the overall survival rates were similar in both groups. TACE might have slowed down disease progression in this group. Further, subgroup analysis showed that HCC patients with extra-hepatic metastases appeared to have a slower disease progression than those with vascular invasion. Regarding of complications in the control and the exceptional groups, there were post-TACE syndrome [47 (83.9%) and 43 (79.6%)], liver decompensation [17 (30.4%) and 16 (29.6%)] and acute liver failure [1 (1.8%) and 3 (5.6%)]. These were similar to previous reports reference. These complication rates were similar in both the control and exceptional groups. TACE did not increase the numbers of procedure-related adverse events in patients with vascular invasion nor in those with extrahepatic metastases (Table 3). Our results indicated that therapy with TACE was safe even in patients with extrahepatic metastases and/or vascular invasion, including partial occlusion of the main portal vein.

Our study had several limitations. First, the study was retrospective, hence some missing data. Second, there were only small numbers of patients in both groups, thus limiting the assessment of prognostic factor values.

Conclusion

The overall median survival of advanced HCC patients who underwent exceptional criteria TACE treatment was comparable to that of standard TACE treatment. Treatment complications were not increased and adequate. Further prospective study with larger sample size is needed to determine the survival benefit in advanced HCC patients.

REFERENCES

1. Yang JD, Roberts LR. Epidemiology and management of hepatocellular carcinoma. Infect Dis Clin North Am 2010;24:899-919, viii.
2. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17.
4. Trevisani F, Magini G, Santi V, *et al*. Impact of etiology of cirrhosis on the survival of patients diagnosed with hepatocellular carcinoma during surveillance. Am J Gastroenterol 2007;102:1022-31.
5. Amon JJ, Nedsuwan S, Chantra S, *et al*. Trends in liver cancer, Sa Kaeo Province Thailand. Asian Pac J Cancer Prev 2005;6:382-6.
6. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519-24.
7. Ikai I, Arii S, Okazaki M, *et al*. Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. Hepatol Res 2007;37:676-91.
8. Fenoglio L, Serraino C, Castagna E, *et al*. Epidemiology, clinical-treatment patterns and outcome in 256 hepatocellular carcinoma cases. World J Gastroenterol 2013;19:3207-16.
9. Dumortier J, Chapuis F, Borson O, *et al.* Unresectable hepatocellular carcinoma: survival and prognostic factors after lipiodol chemoembolisation in 89 patients. Dig Liver Dis 2006; 38:125-33.
10. Lo CM, Ngan H, Tso WK, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
11. Liu CL, Fan ST. Nonresectional therapies for hepatocellular carcinoma. Am J Surg 1997;173:358-65.
12. Trevisani F, Santi V, Gramenzi A, *et al.* Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? Am J Gastroenterol 2007;102: 2448-57; quiz 2458.
13. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
14. Bruix J, Raoul JL, Sherman M, *et al.* Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-9.
15. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembo-

lization improves survival. Hepatology 2003;37:429-42.
16. Nakazawa T, Hidaka H, Shibuya A, *et al.* Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterol 2014;14:84.
17. Takayasu K, Arii S, Ikai I, *et al.* Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131:461-9.
18. Murata S, Mine T, Ueda T, *et al*. Transcatheter arterial chemoembolization based on hepatic hemodynamics for hepatocellular carcinoma. TSWJ 2013;2013:479805.