# Transarterial chemoembolization vs. conservative treatment for unresectable infiltrating hepatocellular carcinoma: A retrospective comparative study

QIANG-SHENG DAI[1*], HONG-LIN GU[2*], SHENG YE[1], YAO-JUN ZHANG[3,4], XIAO-JUN LIN[3,4], WAN YEE LAU[5], ZHEN-WEI PENG[1] and MIN-SHAN CHEN[3,4]

[1]Department of Oncology, The First Affiliated Hospital, Sun Yat-sen University; [2]Guangdong General Hospital, Guangdong Academy of Medical Science; [3]State Key Laboratory of Oncology in Southern China; [4]Department of Hepatobiliary Oncology, Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong; [5]Faculty of Medicine, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, SAR, P.R. China

Received April 30, 2014; Accepted July 23, 2014

DOI: 10.3892/mco.2014.391

**Abstract.** This study was conducted to compare long-term survival between patients with unresectable infiltrating hepatocellular carcinoma (HCC) who were treated with transarterial chemoembolization (TACE) and those who received conservative treatment (best supportive care). Between January, 2007 and January, 2012, a total of 131 consecutive patients with unresectable infiltrating HCC underwent TACE in a cancer center (TACE group), while 156 similar consecutive HCC patients received conservative treatment in another cancer center (conservative treatment group). The diagnosis of unresectable infiltrating HCC was established by agreement between two radiologists coming from the two centers, who performed an independent review of all the cross-sectional imagings of the patients. The two groups were comparable regarding patient characteristics, preoperative liver function, tumor burden and general condition. In the TACE group, 52 patients received one session and 79 patients received more than one session of TACE (mean, 1.5 and range, 1-4 sessions). There was no reported TACE-related mortality. The 1-month mortality rate was 0.8 and 3.8% in the TACE and the conservative groups, respectively (P=0.134). The median survival for the TACE and conservative treatment groups was 7.0 and 3.0 months, respectively. The 6-, 12- and 24-month overall survival rates for the TACE and conservative treatment groups were 61.7, 18.5 and 2.3% vs. 22.7, 12.1 and 0%, respectively (P<0.001). On multivariate analysis, treatment allocation [odds ratio (OR)=1.777; 95% confidence interval (CI): 1.499-2.107; P<0.001] and portal vein tumor thrombosis (OR=1.721; 95% CI: 1.504-1.907; P<0.001) were independent predictors of overall survival. In conclusion, TACE was found to be a safe and feasible treatment option for patients with unresectable infiltrating HCC and it conferred survival benefit over conservative treatment.

*Correspondence to:* Dr Min-Shan Chen, Department of Hepatobiliary Oncology, Cancer Center, Sun Yat-sen University, 651 Dongfeng East Road, Guangzhou, Guangdong 510060, P.R. China
E-mail: chminsh@mail.sysu.edu.cn

Dr Zhen-Wei Peng, Department of Oncology, The First Affiliated Hospital, Sun Yat-sen University, 74 Zhongshan 2nd Road, Guangzhou, Guangdong 510080, P.R. China
E-mail: pengzhenwei2005@163.com; pengzhenwei2005@gmail.com

*Contributed equally

*Key words:* unresectable infiltrating hepatocellular carcinoma, transarterial chemoembolization, conservative treatment, survival, independent predictor

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide (1). Over 600,000 new cases of HCC are officially reported annually worldwide. HCC most commonly arises on a background of chronic liver disease secondary to viral hepatitis, specifically hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, as well as alcoholic and non-alcoholic fatty liver disease (2). Significant geographical variations in the incidence of HCC have been documented, with the highest incidence observed in Asia (3,4). HCC may present with different morphological subtypes, including 'focal/nodular', 'massive' and 'diffuse/infiltrating' (5,6). This gross classification of HCC is primarily based on radiological characteristics. Focal/nodular HCC most commonly presents as an arterially enhancing mass with well-defined margins and a washout pattern during the portal venous phase (7,8). By contrast, infiltrating HCC may be difficult to identify, since it presents as a spreading, ill-defined mass that may blend into the background cirrhotic liver on cross-sectional imaging (7,8). Patients with infiltrating HCC are not good candidates for curative treatment, such as liver resection, liver transplantation or local ablation (9). Sorafenib is the

first targeted therapeutic agent approved for systemic treatment of advanced HCC, on the basis of two randomized, double-blind, placebo-controlled, phase III trials that demonstrated prolonged overall survival (10,11). Sorafenib is recommended for the treatment of advanced and unresectable HCC (12). However, other modalities, such as transarterial chemoembolization (TACE) or transarterial radioembolization using yttrium-90 microspheres are also used to treat infiltrating HCC due to the modest efficacy and high cost of sorafenib treatment (13-15). TACE is currently considered to be one of the standard treatments for patients with unresectable HCC. According to previous randomized controlled studies, TACE exhibited clear survival benefits and improved the quality of life for patients with unresectable HCC when compared to symptomatic supportive care (16,17). Infiltrating HCC cases have seldom been studied as candidates for TACE due to poor demarcation and difficulty in defining the extent of infiltrating HCC on cross-sectional imaging. Recently, a prospective comparative study documented TACE to have worse efficacy for infiltrative compared to focal nodular HCC (18). However, some authors believe that TACE may be beneficial for carefully selected patients with infiltrative HCC (13-15). To the best of our knowledge, the number of comparative studies that have been published to compare TACE with conservative treatment for such patients is limited. We conducted this study to determine whether TACE confers a survival benefit to patients with infiltrative HCC and to uncover the prognostic factors of overall survival.

## Patients and methods

*TACE group*. Between January, 2007 and January, 2012, 131 consecutive patients with infiltrating HCC underwent TACE as initial treatment at the Cancer Center, Sun Yat-sen University. During the same period, 3,914 patients with HCC were treated at the hospital. The patient and tumor characteristics and the presence of underlying liver diseases are summarized in Table I.

*Inclusion criteria*. i) Patient age, 18-75 years; ii) Child-Pugh class A or B liver function (19); iii) Eastern Cooperative Oncology Group (ECOG) performance score ≤2; and iv) HCC with no previous treatment.

*Exclusion criteria*. i) Severe coagulopathy (prothrombin activity <40% or a platelet count <40,000/mm$^3$); ii) Child-Pugh class C liver function or evidence of hepatic decompensation, including ascites, esophageal or gastric variceal bleeding, or hepatic encephalopathy; iv) ECOG scores 3-4; and v) concomitant serious diseases of other organs.

*Diagnosis*. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) scans were used to diagnose infiltrating HCC, as ultrasound was inadequate (20). The diagnosis of infiltrating HCC was established by agreement between two radiologists coming from the two centers participating in this study who performed independent reviewing of the cross-sectional imagings of all the patients.

*TACE*. TACE was performed as previously described (21). In brief, a selective 5 Fr catheter was introduced and visceral angiography was performed to assess the arterial blood supply to the liver and to confirm patency of the portal vein. All the patients underwent a distal super-selective catheterization of the hepatic arteries using a coaxial technique and 2.9 Fr microcatheters (Terumo Corporation, Tokyo, Japan). Subsequently, three chemotherapeutic agents at the same dosage were used throughout this study, regardless of tumor number and size. Hepatic artery infusion chemotherapy was first performed using carboplatin 300 mg (Bristol-Myers Squibb, New York, NY, USA), followed by chemolipiodolization using epirubicin 50 mg (Pharmorubicin; Pfizer, Wuxi, China) and mitomycin C 8 mg (Zhejiang Hisun Pharmaceutical Co., Ltd., Taizhou, China) mixed with 5 ml lipiodol (Lipiodol Ultra-Fluide; Andre Guerbet Laboratories, Aulnay-sous-Bois, France). If the territory of the chemolipiodolized artery did not show stagnant flow, pure lipiodol was then injected. For all cases, embolization was finally performed with absorbable 1-2-mm gelatin sponge particles (Gelfoam; Hangzhou alc Ltd., Hangzhou, China) or 350-560-$\mu$m polyvinyl alcohol particles (Alicon Pharm SCT & TEC Co., Ltd., Hangzhou, China) until stasis was achieved in the tumor-feeding arteries.

*Conservative treatment group*. During the same study period (January, 2007-January, 2012), 156 consecutive patients with infiltrating HCC who had declined sorafenib treatment received conservative treatment (best supportive care) at another cancer center. During the same period, 3,845 patients with HCC were treated in The First Affiliated Hospital of Sun Yat-sen University. The inclusion, exclusion and diagnostic criteria were identical to those in the TACE group. The patient and tumor characteristics and the presence of underlying liver diseases are summarized in Table I.

*Assessment of response*. The response of the tumors to TACE was evaluated using contrast-enhanced CT or MRI at 1 month after treatment. The presence of non-enhanced tumoral areas reflected tissue necrosis. The modified Response Evaluation Criteria in Solid Tumors on CT or MRI were used to measure tumor response (22).

*Follow-up*. Patients in the TACE and conservative treatment groups were followed up monthly for the first year and once every three months thereafter in the outpatient setting using clinical examination, biochemistry and serum α-fetoprotein (AFP) measurements. Contrast-enhanced CT or MRI scans were performed once every 1-2 months for the first year and every 2-3 months thereafter. Bone metastases were excluded by bone scintigraphy on clinical suspicion. In addition, data on the patients' Child-Pugh class and ECOG scores were recorded.

In the TACE group, hepatocellular injury was monitored by serum bilirubin, alanine transaminase, serum albumin (ALB) and prothrombin time. TACE-related complications were evaluated at the end of the first month after treatment. Complications were reported using the National Cancer Institute Common Toxicity Criteria grading, version 4.0 (23). Another session of TACE was performed once every 2-3 months until one of the following end points was reached: i) complete devascularization of the tumor; ii) technical impossibility to embolize the residual tumor, e.g., tumor only

Table I. Patient and tumor characteristics.

| Variables | TACE group (n=131) | Conservative group (n=156) | P-value |
|---|---|---|---|
| Age, years [median (range)] | 55 (20-75) | 55 (23-75) | 0.654 |
| Gender (male/female) | 125/6 | 149/7 | 0.999 |
| HBV (yes/no) | 126/5 | 150/6 | 0.999 |
| HCV (yes/no) | 129/2 | 154/2 | 0.503 |
| AFP, ng/ml [median (range)] | 1,060 (0-138,400) | 1,120 (0-138,400) | 0.078 |
| GGT, U/l (mean ± SD) | 198.0±124.0 | 243±170 | 0.094 |
| AST, U/l (mean ± SD) | 39.2±13.0 | 45.1±17.4 | 0.287 |
| ALT, U/l (mean ± SD) | 65.3±13.5 | 67.7±15.8 | 0.513 |
| ALB, g/l (mean ± SD) | 39.9±7.3 | 37.9±4.9 | 0.060 |
| TBIL, $\mu$mol/l (mean ± SD) | 16.8±6.9 | 17.7±5.5 | 0.159 |
| PT, sec (mean ± SD) | 12.4±0.7 | 12.8±1.0 | 0.364 |
| PLT, 10E9/l (mean ± SD) | 1,120±100 | 101±77 | 0.500 |
| Cirrhosis (yes/no) | 74/57 | 90/66 | 0.999 |
| Child-Pugh classification (A/B) | 109/22 | 123/43 | 0.474 |
| ECOG score (0-1/2) | 109/21 | 120/36 | 0.238 |
| BCLC staging (B/C) | 12/119 | 13/153 | 0.851 |
| CLIP score (2/3/4/5) | 6/36/70/19 | 10/45/72/29 | 0.759 |

TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; GGT, γ-glutamyl transpeptidase; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine transaminase; ALB, albumin; TBIL, total bilirubin; PT, prothrombin time; PLT, platelet; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program.

supplied by extrahepatic collateral arteries; iii) contraindications to TACE; and iv) total resection or ablation of tumor by subsequent surgery or local ablation. Hepatic resection or local ablation were performed as previously described (24,25). In cases with ii) or iii), it was recommended that the patients received sorafenib. If they refused, conservative treatment was administered.

*Statistical analysis*. Statistical analyses were performed using the SPSS 10.0 statistical software (SPSS, Inc., Chicago, IL, USA). Comparisons between the two groups were performed using the Student's t-test for continuous data and the Chi-square test for categorical data. Overall survival was calculated using a life table method and compared with the Mantel-Cox test. The survival curves were constructed with the Kaplan-Meier method and compared using the log-rank test. The relative prognostic significance of the variables in predicting overall survival rates was assessed using the multivariate Cox proportional hazards regression analysis. The results are presented as means ± standard deviation, or median and range. All the statistical tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Patient characteristics*. A total of 287 patients were recruited in this study (TACE group, n=131; and conservative treatment group, n=156). The characteristics of the patients are summarized in Table I. The two groups were comparable regarding patient characteristics, preoperative liver function and general condition (Table I). Following treatment, 47 patients in the TACE and 62 patients in the conservative treatment group received nucleoside-analog treatment for HBV (P=0.735).

*Radiographic characteristics*. In all infiltrating HCCs, the margins of the tumors were poorly demarcated. The median infiltrating HCC diameter was 9.0 and 9.8 cm for the TACE and conservative treatment groups, respectively. The majority of the patients in the two groups had radiographic evidence of macrovascular invasion at the time of the diagnosis of infiltrating HCC (TACE vs. conservative treatment group, 89/131 vs. 126/156, respectively; P=0.364). All patients with macrovascular invasion had some degree of portal vein tumor thrombosis (PVTT). In the TACE group, 22.9% of the patients had main portal vein involvement, whereas 45% had involvement of the right and/or the left hemihepatic portal and/or sectional/segmental portal vein. In the conservative treatment group, 23.1% of the patients had main portal vein involvement, whereas 57.7% had involvement of the right and/or left hemihepatic portal and/or sectional/segmental portal vein. In addition to portal vein tumor thrombi, 12 and 16 of the patients in the TACE and conservative treatment groups exhibited tumor invasion of the hepatic vein(s), respectively (P=0.844). On further analysis, 6 and 9 of the patients had the tumor thrombi extending into the main hepatic vein(s), 6 and 7 into the inferior vena cava and 3 and 4 extended into the right atrium in the TACE and the conservative treatment groups, respectively. A total of 89 and 97 infiltrating HCC lesions displayed early arterial hyper-enhancement in the TACE and the conservative treatment groups (67.9 vs. 62.2%, respectively; P=0.706). All

Table II. Radiographic and pathological characteristics of patients with infiltrating HCC at the time of diagnosis.

| Variables | TACE group (n=131) | Conservative group (n=156) | P-value |
|---|---|---|---|
| Maximum tumor size, cm (mean ± SD) | 9.0±2.5 | 9.8±1.0 | 0.070 |
| Vascular invasion | 89 | 126 | 0.364 |
| Portal vein | | | 0.488 |
| Main | 30 | 36 | |
| Hemihepatic | 37 | 61 | |
| Sectional/segmental | 22 | 29 | |
| Main/hemihepatic portal vein obstruction (yes/no) | 19/112 | 23/134 | 0.999 |
| Hepatic vein invasion | 12 | 16 | 0.844 |
| Hepatic vein only | 6 | 9 | |
| Inferior vena cava | 6 | 7 | |
| Right atrium | 3 | 4 | |
| Arterial hyper-enhancement (yes/no) | 89/42 | 97/59 | 0.706 |
| Intrahepatic metastases (yes/no) | 67/64 | 79/77 | 0.999 |
| Distant metastases | 39 | 47 | 0.999 |
| Lung | 24 | 30 | |
| Lymph nodes | 13 | 15 | |
| Bone | 1 | 1 | |
| Adrenal | 1 | 1 | |
| Biliary duct dilation | 13 | 14 | 0.999 |
| Hemihepatic | 9 | 7 | |
| Segmental | 2 | 3 | |
| Whole liver | 2 | 4 | |
| MRI T2 signal appearance | 30 | 45 | 0.528 |
| Hyperintense | 22 | 31 | |
| Isointense | 8 | 14 | |

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; MRI, magnetic resonance imaging.

these lesions demonstrated washout during the portal venous phase. At the time of diagnosis of infiltrating HCC, 51.1 and 50.64% of the patients exhibited intrahepatic satellite lesions and 29.8 and 30.1% had extrahepatic metastases, respectively (P=0.999 and P=0.999, respectively). The most common metastatic sites in the TACE and conservative treatment groups were the lungs (18.3 vs. 19.2%, respectively) and lymph nodes (10.8 vs. 10.3%, respectively). Intrahepatic biliary ductal dilatation was found in 9.9 and 9.6% in the TACE and conservative treatment groups, respectively (P=0.999). There were 30 and 45 patients in the TACE and the conservative treatment groups who received a liver MRI (P=0.528). Among these patients, 22 (73.0%) in the TACE and 31 (69.0%) tumors in the conservative treatment group exhibited relative homogeneity and mild hyperintensity on T2-weighted images. The remaining tumors exhibited isointensity to the surrounding liver parenchyma (Table II).

*Outcomes of TACE*. In the TACE group, 131 patients received a mean of 1.5 sessions (range, 1-4 sessions) of TACE. Of those patients, 52 (39.7%) received one session and 79 (60.3%) received more than one sessions of TACE. The initial TACE consisted of the injection of anticancer drugs, lipiodol and gelatin sponge particles in 10 of 19 (52.6%) patients with main/hemihepatic portal vein invasion and portal vein obstruction, 43 of 70 (61.4%) patients with main/hemihepatic portal vein invasion, but without portal vein obstruction, and 27 of 59 (45.8%) patients with sectional/segmental PVTT. The remaining 42 patients received anticancer drugs and lipiodol injection only.

The tumor response and complications in the two groups are shown in Tables III and IV, respectively. All the TACE-related complications were successfully managed with conservative treatment. The 1-month mortality rate was 0.8 and 3.8% in the TACE and conservative groups, respectively (P=0.134).

Following TACE, the tumors in 6 patients were downstaged and suitable for partial hepatectomy (n=6) or local ablative therapy (radiofrequency ablation, n=1; or radiofrequency + percutaneous ethanol injection, n=1). Thirteen patients with tumor progression following TACE received sorafenib treatment.

*Survival outcomes*. At a median follow-up of 6.0 months (range, 1-59 months), 285 patients (94.9%) had succumbed to the disease. The overall median survival was 5.0±0.35 months [95% confidence interval (CI): 4.32-5.68 months]. The 6-, 12-

Table III. Tumor response in the transarterial chemoembolization (TACE) and conservative treatment groups.

| Type of response | TACE group (n=131) | Conservative group (n=156) | P-value |
|---|---|---|---|
| Complete response | 0 | 0 | - |
| Partial response | 21 | 0 | <0.001 |
| Stable disease | 52 | 33 | 0.014 |
| Progressive disease | 58 | 123 | 0.004 |

Table IV. Complications in the transarterial chemoembolization (TACE) and conservative groups.

| Complications | TACE group (n=131) | Conservative group (n=156) | P-value |
|---|---|---|---|
| TACE-related | | | |
| Postembolization syndrome | 97 | 0 | <0.001 |
| Cholecystitis | 1 | 0 | 0.452 |
| Anemia/thrombocytopenia | 1 | 0 | 0.452 |
| Temporary liver decompensation | 42 | 0 | <0.001 |
| Disease-related (at 1 month) | | | |
| Spontaneous rupture | 0 | 1 | 0.999 |
| Variceal bleeding | 0 | 1 | 0.999 |
| Progressive liver failure | 0 | 1 | 0.999 |
| Procedure-related mortality | 0 | 0 | 0.999 |
| 1-month mortality | 1 | 6 | 0.134 |

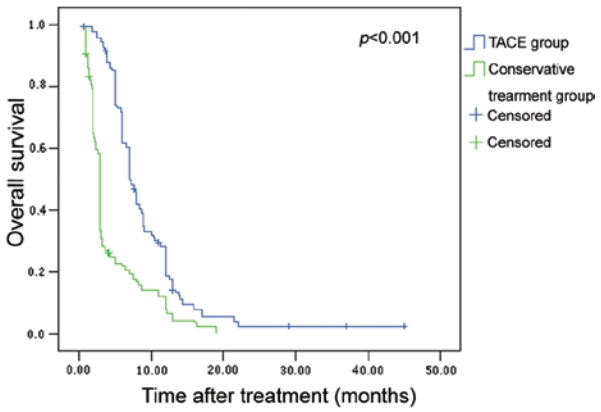


Figure 1. Overall survival for patients with infiltrating hepatocellular carcinoma who received transarterial chemoembolization (TACE) or conservative treatment. The 6-, 12- and 24-month overall survival rates for the TACE and conservative treatment groups were 61.7, 18.5 and 2.3% vs. 22.7, 12.1 and 0%, respectively. The TACE group exhibited significantly better overall survival compared to the conservative group (P<0.001).

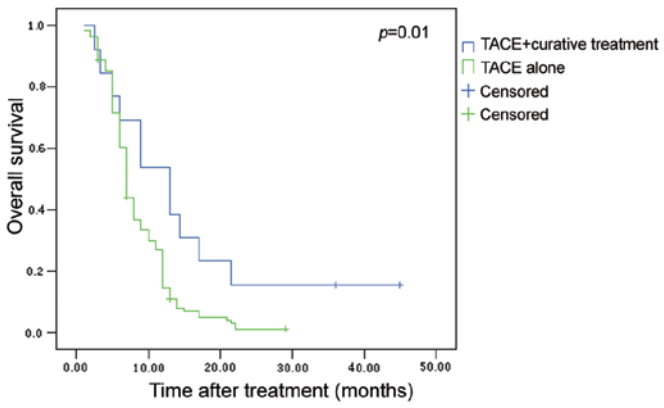


Figure 2. Overall survival for patients who received curative treatment after tumor downstaging with transarterial chemoembolization (TACE) and patients who received TACE alone. The 6-, 12- and 24-month overall survival rates for TACE + curative treatment and TACE alone were 69.2, 53.8 and 15.4% vs. 60.4, 14.4 and 1%, respectively. The difference was statistically significant (P=0.01).

and 24-month overall survival rates for all the patients were 41.9, 12.9 and 1.1%, respectively. The median survival for the TACE and the conservative treatment groups was 7.0±0.3 and 3.0±0.1 months, respectively (P<0.001). The 6-, 12- and 24-month overall survival rates for the TACE and the conservative treatment groups were 61.7, 18.5 and 2.3% vs. 22.7, 12.1 and 0%, respectively. The TACE group exhibited significantly better overall survival compared to the conservative group (P<0.001, Fig. 1).

In the TACE group, the median survival for the 8 patients who were downstaged to receive potentially curative treatments and the remaining 123 patients was 13.0±3.07 and 7.0±0.27 months, respectively. The 6-, 12- and 24-month overall survival rates for TACE + curative treatment and TACE alone were 69.2, 53.8 and 15.4 vs. 60.4, 14.4 and 1%, respectively. The difference was significant (P=0.01, Fig. 2). The median survival for the 13 patients who received sorafenib and

Table V. Univariate and multivariate analysis of prognostic factors.

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Variables | P-value | OR | 95% CI | P-value |
| Age, years (60 vs. >60) | 0.01 | | | |
| Gender (male vs. female) | | | | |
| HBV (yes vs. no) | | | | |
| HCV (yes vs. no) | | | | |
| AFP, ng/ml (≤400 vs. >400) | | | | |
| GGT, U/l (≤50 vs. >50) | 0.009 | | | |
| AST, U/l (≤40 vs. >40) | | | | |
| ALT, U/l (≤40 vs. >40) | | | | |
| ALB, g/l (≤35 vs. >35) | 0.018 | | | |
| TBIL, μmol/l (≤20 vs. >20) | | | | |
| PT, sec (≤13.5 vs. >13.5) | | | | |
| PLT, 109/l (≤100 vs. >100) | | | | |
| PVTT type (segmental vs. main/hemiliver) | <0.001 | 1.721 | 1.504-1.907 | <0.001 |
| Maximum tumor size, cm (≤10.0 vs. >10.1) | <0.001 | | | |
| Cirrhosis (yes vs. no) | | | | |
| ECOG (0-1 vs. 2) | | | | |
| Child-Pugh classification (A vs. B) | | | | |
| Treatment allocation (TACE vs. conservative treatment) | <0.001 | 1.777 | 1.499-2.107 | <0.001 |

OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; GGT, γ-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine transaminase, ALB, albumin; TBIL, total bilirubin; PT, prothrombin time; PLT, platelet; PVTT, portal vein tumor thrombosis; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization.

the remaining 118 patients was 7.1±0.86 and 6.9±0.42 months, respectively (P=0.563).

*Survival factor analysis*. On univariate analysis, 6 factors were correlated with survival, namely age, serum γ-glutamyl transpeptidase, serum ALB, PVTT type, maximum tumor size and treatment allocation (Table V). On multivariate analysis, only treatment allocation [odds ratio (OR)=1.777; 95% CI: 1.499-2.107; P<0.001] and PVTT type (OR=1.721; 95% CI: 1.504-1.907; P<0.001) were independent predictors of overall survival.

## Discussion

Infiltrating HCC has not been adequately investigated, as it is difficult to diagnose and measure on cross-sectional images. However, infiltrating HCC is not rare (5,6). As liver resection and transplantation are not treatment options for the majority of patients with infiltrating HCC, TACE and other locoregional treatments have been advocated as potential therapeutic options (15,18). Lopez *et al* (18) reported on a small series (n=19) of patients with infiltrating HCC who underwent TACE. In that study, the authors compared patients with focal vs. those with infiltrating HCC who underwent conventional TACE. Of note, the authors reported more procedure-related mortalities among patients with infiltrating HCC (16% of the patients succumbed within 30 days of TACE) and recommended caution in utilizing intra-arterial therapy (IAT) for patients with infiltrating HCC due to the high periprocedural mortality rate. By contrast, in this study, TACE was found to be relatively safe and well-tolerated. By using a large cohort of patients with infiltrating HCC, this study was the first comparative study to demonstrate a significantly improved overall survival for patients treated with TACE when compared to patients treated conservatively (P<0.001).

Of the 131 patients, 8 (6.1%) underwent potentially curative treatment after tumor downstaging and their survival was significantly superior to that of the remaining 123 patients in the TACE group (P=0.01). This result indicated that salvage procedures after tumor downstaging are beneficial for those patients who present initially with unresectable HCC (26-28). The main problem with tumor downstaging in infiltrating HCC is that only a small proportion of patients respond well enough to treatment to allow salvage liver resection or percutaneous ablative procedures and the responders cannot be predicted. In our study, 13 patients with tumor progression after TACE received sorafenib treatment. Patients who received combined TACE and sorafenib did not exhibit a survival superior to that of the remaining 118 patients who received TACE alone (P=0.542). However, it is difficult to determine the true role of sorafenib in this study, since it was used as a salvage treatment for patients with infiltrating HCC when there was tumor progression after TACE. In addition, only a small number of patients received sorafenib after TACE in this study.

The combination of carboplatin, doxorubicin and mitomycin C is the most commonly used drug combina-

tion regimen used in TACE (29). In this study, there was no significant difference in the 1-month mortality rate between the TACE (0.8%) and the conservative groups (3.8%, P=0.134). TACE-related complications were adequately managed using non-operative treatment, thus suggesting that TACE is a safe treatment option for patients with infiltrating HCC.

Recently, a study by Kneuertz *et al* (14) on patients treated with IAT, reported that their median overall survival was longer compared to that of patients who received best supportive care (12 vs. 3 months, respectively; P=0.001), with a periprocedural mortality of 2.7% after TACE. In addition, the survival of patients after IAT was similar for patients with infiltrating or multifocal HCC (P=0.27). The authors concluded that IAT for infiltrating HCC was safe and was associated with a survival comparable to that of patients with multifocal HCC. Thus, infiltrating HCC is no longer considered a contraindication to IAT in selected patients. The survival benefit after TACE in the Kneuertz *et al* (14) study was better compared to that in our study. However, in that study, the IAT group had significantly lower AFP levels (244 vs. 1,563 ng/ml) and 25 of the 48 patients (52.1%) received periprocedural sorafenib in addition to IAT. As low AFP levels and sorafenib are associated with improved survival, these factors were likely to contribute to the 9-month survival benefit as observed among patients with infiltrating HCC who received IAT in the Kneuertz *et al* study (14). In another study conducted by Mehta *et al* (15), the outcomes, effects of treatment and prognostic factors were assessed in a large cohort of patients with infiltrating HCC (n=155). In that study, 11.8% (18/152) patients received TACE and these patients exhibited a significantly better survival (P=0.0002) compared to those who did not receive tumor-directed therapy (n=109). The authors concluded that patients may derive survival benefit from TACE, although further investigations are required (15).

Our study had several limitations. The main limitation was the retrospective, non-randomized study design. Several confounding factors may have affected our findings. Furthermore, only a small number of patients received sorafenib in this study and patients may achieve better results with sorafenib therapy. It is also possible that our results may not apply to patients with infiltrating HCC in other countries, due to differences in demographics and underlying causes of liver disease. Despite these limitations, however, our data represent the largest patient cohort in the literature that allows better characterization of the clinical and radiological characteristics, outcomes and prognostic factors associated with unresectable infiltrating HCC treated with TACE or conservative treatment.

In conclusion, the present study demonstrated that TACE is a safe treatment option for patients with unresectable infiltrating HCC and patients achieved better survival with TACE rather than with conservative treatment. However, further prospective studies are required to confirm the efficacy and safety of TACE for patients with infiltrating HCC.

## Acknowledgements

This study was supported by a grant from the National Natural Science Foundation of China (no. 81301842), the Outstanding Young Scientist Award of First Affiliated Hospital of Sun Yat-sen University (2013-2017), the Outstanding Young Scientist Award of Guangzhou (2014), the State Key Project on Infectious Diseases of China (no. 2012ZX10002-016), the 5010 Foundation of Sun Yat-sen University (no. 2007043) and the Science and Technology Planning Project of Guangdong Province (no. 2012B031800032).

## References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin 61: 69-90, 2011.
2. Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108, 2005.
3. Llovet JM, Burroughs A and Bruix J: Hepatocellular carcinoma. Lancet 362: 1907-1917, 2003.
4. El-Serag HB: Hepatocellular carcinoma. N Engl J Med 365: 1118-1127, 2011.
5. Trevisani F, Caraceni P, Bernardi M, *et al*: Gross pathologic types of hepatocellular carcinoma in Italian patients. Relationship with demographic, environmental and clinical factors. Cancer 72: 1557-1563, 1993.
6. Okuda K, Peters RL and Simson IW: Gross anatomic features of hepatocellular carcinoma from three disparate geographic areas. Proposal of new classification. Cancer 54: 2165-2173, 1984.
7. Lencioni R, Crocetti L, Della Pina MC and Cioni D: Guidelines for imaging focal lesions in liver cirrhosis. Expert Rev Gastroenterol Hepatol 2: 697-703, 2008.
8. Kanematsu M, Semelka RC, Leonardou P, Mastropasqua M and Lee JK: Hepatocellular carcinoma of diffuse type: MR imaging findings and clinical manifestations. J Magn Reson Imaging 18: 189-195, 2003.
9. Demirjian A, Peng P, Geschwind JF, *et al*: Infiltrating hepatocellular carcinoma: seeing the tree through the forest. J Gastrointest Surg 15: 2089-2097, 2011.
10. Llovet JM, Ricci S, Mazzaferro V, *et al*; SHARP Investigators Study Group: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359: 378-390, 2008.
11. Cheng AL, Kang YK, Chen Z, *et al*: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10: 25-34, 2009.
12. Forner A, Reig ME, de Lope CR and Bruix J: Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30: 61-74, 2010.
13. Jang ES, Yoon JH, Chung JW, *et al*: Survival of infiltrative hepatocellular carcinoma patients with preserved hepatic function after treatment with transarterial chemoembolization. J Cancer Res Clin Oncol 139: 635-643, 2013.
14. Kneuertz PJ, Demirjian A, Firoozmand A, *et al*: Diffuse infiltrative hepatocellular carcinoma: assessment of presentation, treatment, and outcomes. Ann Surg Oncol 19: 2897-2907, 2012.
15. Mehta N, Fidelman N, Sarkar M and Yao FY: Factors associated with outcomes and response to therapy in patients with infiltrative hepatocellular carcinoma. Clin Gastroenterol Hepatol 11: 572-578, 2013.
16. Lo CM, Ngan H, Tso WK, *et al*: Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35: 1164-1171, 2002.
17. Llovet JM, Real MI, Montana X, *et al*: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359: 1734-1739, 2002.
18. Lopez RR Jr, Pan SH, Hoffman AL, *et al*: Comparison of transarterial chemoembolization in patients with unresectable, diffuse vs. focal hepatocellular carcinoma. Arch Surg 137: 653-658, 2002.
19. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC and Williams R: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60: 646-649, 1973.
20. Myung SJ, Yoon JH, Kim KM, *et al*: Diffuse infiltrative hepatocellular carcinomas in a hepatitis B-endemic area: diagnostic and therapeutic impediments. Hepatogastroenterology 53: 266-270, 2006.
21. Shi M, Chen JA, Lin XJ, *et al*: Transarterial chemoembolization as initial treatment for unresectable hepatocellular carcinoma in southern China. World J Gastroenterol 16: 264-269, 2010.
22. Lencioni R and Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30: 52-60, 2010.

23. National Cancer Institute: Common terminology criteria for adverse events (CTCAE), version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_ 2010-06-14_QuickReference_5x7.pdf. Accessed June 14, 2010.
24. Shi M, Guo RP, Lin XJ, *et al*: Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg 245: 36-43, 2007.
25. Chen MS, Li JQ, Zheng Y, *et al*: A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 243: 321-328, 2006.
26. Lau WY, Leung TW, Lai BS, *et al*: Preoperative systemic chemoimmunotherapy and sequential resection for unresectable hepatocellular carcinoma. Ann Surg 233: 236-241, 2001.
27. Lau WY, Ho SK, Yu SC, Lai EC, Liew CT and Leung TW: Salvage surgery following downstaging of unresectable hepatocellular carcinoma. Ann Surg 240: 299-305, 2004.
28. Lau WY and Lai EC: Salvage surgery following downstaging of unresectable hepatocellular carcinoma - a strategy to increase resectability. Ann Surg Oncol 14: 3301-3309, 2007.
29. Lau WY, Yu SC, Lai EC and Leung TW: Transarterial chemoembolization for hepatocellular carcinoma. J Am Coll Surg 202: 155-168, 2006.