

# Survival benefit of transcatheter arterial chemoembolization in patients with hepatocellular carcinoma larger than 10 cm in diameter

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## SUMMARY

### Background

The safety and survival benefit of transcatheter arterial chemoembolization for patients with huge hepatocellular carcinoma is uncertain.

### Aim

To evaluate the role of embolization in unresectable hepatocellular carcinomas larger than 10 cm.

### Methods

Twenty-six consecutive patients who had an unresectable hepatocellular carcinoma larger than 10 cm and refused aggressive treatment, were enrolled as the control group. Another 31 patients matching with the control cases and undergoing embolization for huge unresectable hepatocellular carcinoma served as the embolization group. Survival between the two groups was compared.

### Results

Two patients (7%) died from embolization-related complications. Patients in embolization group had longer survival than those in control group (median survival: 9.13 vs. 2.1 months). The 1-, 3- and 5-year survival rates in embolization group were 42%, 13% and 7% respectively. The 1- and 3-year survival rates for patients in control group were 8% and 0% respectively. In multivariate analysis, embolization and prothrombin ratio  $\leq 1.2$  were two independent factors associated with a better survival.

### Conclusions

Embolization-related mortality is low for huge hepatocellular carcinoma, and the technique provides survival benefit in patients with unresectable hepatocellular carcinomas larger than 10 cm in diameter.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is prevalent in Asia, and its incidence is increasing in Western countries.<sup>1, 2</sup> Regular screening programmes for high-risk patients are a routine study to detect HCC in Taiwan.<sup>3</sup> Although, advanced HCCs larger than 10 cm in diameter during diagnosis are still often seen. Surgical resection is the only way to cure the disease for patients with big tumours.<sup>4–7</sup> However, huge tumours frequently present with poor liver reserve, vascular invasion and intrahepatic dissemination, all the factors limit the resectability of huge HCC. Transcatheter arterial chemoembolization (TACE) is a main palliative treatment for unresectable HCC. For unresectable HCC larger than 10 cm in diameter, TACE is the only treatment option. However, TACE could give rise to excessive liver damage for huge HCCs. This treatment option must be weighed against the benefit of antitumour effectiveness and the risk of liver decompensation before making the decision of TACE in clinical practice. In addition, larger tumour size is an independent poor prognostic factor in both resectable and unresectable HCC, and the risk of complications by TACE for huge tumours is high.<sup>8–10</sup> One recent study suggests that patients with HCC larger than 10 cm in diameter are not suitable candidates for TACE treatment because of a high mortality rate.<sup>10</sup> Whether TACE is beneficial or not for this type of patient deserves further study.

There are only a limited number of reports to date focusing on TACE for patients with HCC larger than 10 cm in diameter. Consequently, we conducted this retrospective, case-control study to elucidate the role of TACE for patients with huge unresectable HCC.

## MATERIALS AND METHODS

From July 1992 to June 1996, 26 consecutive patients with unresectable HCC larger than 10 cm in diameter during diagnosis at three medical centres (National Taiwan University Hospital, Taipei, Taiwan; Taipei Veterans General Hospital, Taipei, Taiwan and Kaohsiung Medical University Hospital, Kaohsiung, Taiwan), who were eligible for TACE but refused aggressive treatment, were enrolled as index cases (control group) in this study. The medical records of these cases had been carefully reviewed to confirm that their doctors had suggested TACE as the primary treatment for them. As the age (30–77 years) and

tumour size (10.2–24 cm) were rather heterogeneous among the patients, we selected TACE cases that could match with the age, tumour pattern and underlying liver function of each index case. All the selected patients had undergone TACE for the unresectable huge HCC during the same period in each hospital. The selection criteria for TACE treatment group included: (i) the age difference with corresponding index case was <5 years; (ii) the tumour size difference with corresponding index case was within 2 cm in diameter; (iii) the tumour number was equal to that of corresponding index case; (iv) the treatment modality was TACE only without other adjuvant treatments, such as percutaneous ethanol injection treatment; and (v) the underlying liver function matched with that of corresponding index case in Child–Pugh classification. To avoid selection bias in the TACE group, all cases, which fulfilled the selection criteria, were enrolled. There were 31 patients matching the criteria and served as the TACE treatment group. The diagnosis of HCC for all the 57 cases was confirmed either by biopsy or by alpha-fetoprotein (AFP) assay  $\geq 400$  ng/mL, accompanied with focal lesions from at least two image examinations (sonography, computerized scan and coeliac angiography) associated with progressive course of tumours (increasing size and number).<sup>8, 9</sup> All patients fulfilled the following criteria for TACE: (i) no main portal vein trunk involvement or extrahepatic metastasis; (ii) Child–Pugh functional class A or B; (iii) normal renal function with a serum creatinine concentration <1.6 mg/dL; (iv) no gross ascites by ultrasound; and (v) platelet count  $>60 \times 10^9/L$ .<sup>9, 11</sup> The performance status of the cases was assessed according to the performance status test (PST) for cancer patients.<sup>12, 13</sup>

Transcatheter arterial chemoembolization was carried out through selective hepatic arterial catheterization; whenever possible, the arteries supplying the tumours were catheterized superselectively followed by infusion of a mixture of 20–30 mg adriamycin (Farmitalia Carlo Erba, Milan, Italy) and 5–10 mL of lipiodol (Laboratoire Guerbet, Paris, France). The feeding arteries were then embolized with 2–3 mm strips of gelfoam (Upjohn Co., Kalamazoo, MI, USA).<sup>9, 14</sup> All cases were assessed for tumour response by AFP assay, sonography and/or computerized scan 2–3 months after TACE. In cases of viable or recurrent tumours, subsequent TACE was arranged if patients still fulfilled the criteria of TACE. All patients were followed regularly at least every 3–6 months after diagnosis.

The survival status of the studied patients was obtained from hospital records and further confirmed by The mortality databank established by the statistics office, DOH, Republic of China (Taiwan). The mortality databank is based on data from the certificate of death, which contains time, place and cause of death, and details of the person who issued the document.<sup>8</sup>

### Statistical analysis

The Wilcoxon rank sum test and Student's *t*-test or chi-squared test were used where appropriate for the comparison of variables between groups. Cumulative survival rate was obtained by using the Kaplan–Meier method.<sup>15</sup> Survival curves were statistically compared using the log rank test. Variables that achieved statistical significance ( $P < 0.05$ ) or close to significance ( $P < 0.1$ ) in the univariate analysis were subsequently included in a multivariate analysis using a stepwise

forward Cox regression procedure.<sup>16</sup> For all tests, a *P*-value of  $<0.05$  was considered significant.

## RESULTS

### Characteristics of patients with unresectable HCC larger than 10 cm in diameter

The characteristics of patients in the TACE group and the control group were comparable in age, sex, tumour size, AFP levels, serum albumin, creatinine, total bilirubin, alanine transaminase levels, prothrombin time, the proportion of vascular invasion, and the distribution of multinodular tumours, Child–Pugh classification and Cancer of the Liver Italian Program (CLIP) scores (Table 1). Most of the patients were infected by hepatitis B virus. Antihepatitis C virus data were not available for some patients because the assay was not widely used to survey HCC in the early 1990s. The

**Table 1.** Characteristics of the studied patients undergoing TACE or conservative treatment

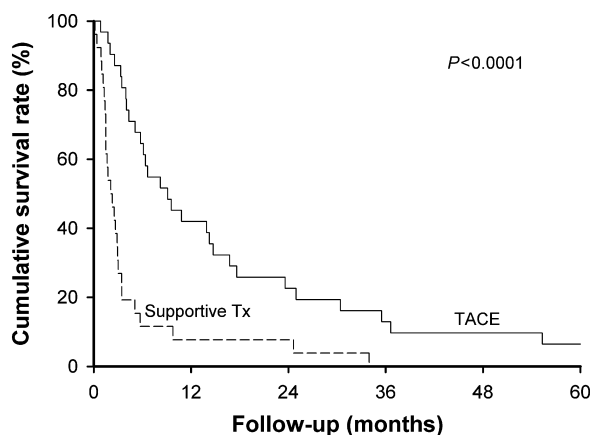
	TACE ( <i>n</i> = 31)	Control ( <i>n</i> = 26)	<i>P</i> -value
Age (mean ± s.d.)	59.5 ± 12.9	57.7 ± 13.3	0.609
Sex (m:f)	28:3	25:1	0.617
Multinodular tumours (%)	12 (38.7)	11 (42.3)	0.996
Tumour size			
Mean ± s.d.	13.4 ± 3.5	12.9 ± 3.7	0.589
Median; range	12 (10.4–22)	11 (10.2–24)	
AFP (ng/mL) (median; range)	582 (3–313 020)	576 (3–250 000)	0.993
Albumin (g/dL)	3.5 ± 0.4	3.5 ± 0.6	0.816
Serum creatinine (mg/dL)	0.98 ± 0.29	0.96 ± 0.30	0.908
Total bilirubin (mg/dL)	1.31 ± 0.68	1.39 ± 0.55	0.225
Alanine transaminase (U/L)	115.2 ± 151.8	125.5 ± 126.1	0.475
Prothrombin time (INR)	1.08 ± 0.1	1.14 ± 0.2	0.201
Vascular invasion (%)	10 (32.3)	14 (53.8)	0.169
Child–Pugh			
A	23 (74.2)	20 (76.9)	1.0
B (%)	8 (25.8)	6 (23.1)	
Performance status test (PST, %)			
0	2 (6.5)	1 (3.8)	0.933
1	24 (77.4)	21 (80.7)	
2	3 (9.6)	3 (11.5)	
3	2 (6.5)	1 (3.8)	
No. of CLIP score			
2 (%)	13 (41.9)	9 (34.6)	0.403
3	10 (32.3)	6 (23.1)	
4	7 (22.6)	7 (26.9)	
5	1 (3.2)	4 (15.4)	
HBsAg positive (%)	18/29 (62.1)	18/25 (72)	0.629
Anti-HCV positive (%)	3/19 (15.8)	2/11 (18.2)	1.0

TACE, transcatheter arterial chemoembolization; AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; INR, international normalized ratio.

performance status of the majority of patients was between PST 0 and 2. Two patients in the TACE group and one patient in the control group had PST = 3. There was no statistical difference in the status of PST between the two groups.

### Comparison of survival between the TACE and the control (supportive) group (Figure 1)

There were total 59 courses of TACE applied for the 31 patients in the treatment group, with each patient receiving a mean of 1.9 courses (range: 1–6). TACE for tumour larger than 10 cm in diameter was rather safe, only two patients (6.5%) died from TACE-related complications. One died from liver decompensation and survived for 1.73 months after TACE. The other died from acute renal failure and survived for 0.86 months after TACE. Among the 57 patients who had unresectable HCC larger than 10 cm in diameter, patients in the TACE group had longer a survival rate than those in the control group ( $P < 0.0001$ , Figure 1). The median survival for patients who underwent TACE was 9.13 months [95% confidence interval (CI): 4.3–13.97 months], which was significantly longer than 2.1 months for the control group (95% CI: 1.02–3.18 months). The 1-, 2-, 3-, 4- and 5-year survival rates in TACE group were 41.9%, 22.6%, 12.9%, 9.7% and 6.5% respectively. The 1-, 2- and 3-year survival rates for patients in control group were 7.7%, 7.7%



Patients at risk						
	0	12	24	36	48	60
TACE	31	13	7	4	2	2
Supportive Tx	26	2	2	0		

Figure 1. Cumulative survival of patients with unresectable hepatocellular carcinoma undergoing transcatheter arterial chemoembolization or supportive treatment.

and 0% respectively. No patients could survive longer than 3 years without treatment.

### Univariate and multivariate analyses of factors associated with survival

Among the 57 patients with unresectable HCC larger than 10 cm in diameter, total bilirubin  $< 1.6$  mg/dL, prothrombin time [international normalized ratio (INR)]  $\leq 1.2$  and TACE treatment were factors associated with longer survivals in univariate analysis (Table 2). Tumour-related factors, such as tumour number and size, and vascular invasion were not associated with survival for patients with huge HCC. However, liver reserve was associated with survival for these patients. CLIP score was not related to survival in patients with huge HCC. In multivariate analysis, TACE and prothrombin time (INR)  $\leq 1.2$  was still significantly associated with a better survival rate (Table 3).

### DISCUSSIONS

The treatment option for HCC larger than 10 cm in diameter is limited. Surgical resection can provide survival benefit for patients with solitary HCC larger than 10 cm in diameter with well-preserved liver function but without venous invasion.<sup>5, 6</sup> However, the resectability rate for patients with advanced HCC is low. TACE is a main treatment for unresectable HCC. The survival benefit of TACE for patients with unresectable HCCs has remained undetermined until recently, in that one meta-analysis study and one nation-wide multi-centre study confirmed the positive role of TACE.<sup>9, 17</sup> However, only less than one-fifth of patients with unresectable HCC had tumours larger than 10 cm in diameter in Taiwan.<sup>9</sup> Studies rarely discussed the topic of TACE for this specific group of patients.

The complications of TACE include postembolization syndromes, postprocedural pain, worsening of hepatic function, hepatic failure and renal failure.<sup>18–22</sup> The chance of complications induced by TACE could be higher for patients with huge tumours. In a recent study which evaluated TACE for patients with unresectable HCC; tumour size larger than 10 cm in diameter was an independent poor prognostic factor.<sup>10</sup> A high TACE-related mortality rate (20%) was observed among patients with tumours larger than 10 cm and lower serum albumin level.<sup>10</sup> Whether the pros of antitumour effect can counteract the cons of complications generated by TACE deserves further

**Table 2.** Univariate analysis of factors associated with survivals

Variables	Patient numbers	Median survivals (months) (95% CI)	P-value
Age			
≤60-year old	28	3.43 (0–7.11)	0.5106
>60-year old	27	4.33 (1.52–7.15)	
Sex			
Male	53	4.03 (2.3–5.77)	0.7255
Female	4	3.33 (0–17.77)	
Albumin			
≤3.5 g/dL	32	3.47 (2.22–4.71)	0.4608
>3.5 g/dL	25	5.13 (0.67–9.59)	
Bilirubin			
<1.6 mg/dL	41	5.73 (3.47–7.99)	0.0561
≥1.6 mg/dL	16	2.83 (1.81–3.25)	
ALT			
≤100 U/L	37	3.97 (2.89–5.04)	0.2548
>100 U/L	20	6.63 (0–14.03)	
Prothrombin time (INR)			
≤1.2	44	5.07 (2.79–7.34)	0.0026
>1.2	13	1.77 (1.17–2.37)	
Creatinine			
≤1.2 mg/dL	47	4.33 (2.09–6.57)	0.5852
>1.2 mg/dL	10	2.97 (0–6.47)	
Child			
A	43	5.07 (1.98–8.15)	0.4094
B	14	3.47 (3.41–3.53)	
Single tumour	34	5.73 (2.35–9.11)	0.2634
Multinodular tumours	23	3.43 (2.55–4.32)	
Tumour size			
≤15 cm	47	5.07 (2.02–8.11)	0.4220
>15 cm	10	2.57 (1.33–3.81)	
Vascular invasion			
Yes	24	2.53 (0.89–4.17)	0.4559
No	33	5.13 (2.77–7.50)	
AFP			
≤400 ng/mL	24	5.13 (2.53–7.73)	0.4803
>400 ng/mL	33	3.47 (2.08–4.85)	
CLIP score			
2–3	38	5.13 (2.41–7.85)	0.2924
4–5	19	3.43 (2.19–4.68)	
Treatment TACE	31	9.13 (4.3–13.97)	<0.0001
Supportive	26	2.1 (1.02–3.18)	

ALT, alanine transaminase; CI, confidence interval; TACE, transcatheter arterial chemoembolization; AFP, alpha-fetoprotein; INR, international normalized ratio.

study. A randomized controlled study is ideal to identify the role of TACE for huge unresectable HCC, but it is not ethical to leave patients untreated during randomization. In this study, the 26 patients in the control group, from three medical centres over a 4-year interval, represented the natural course of huge unresectable HCC. All these patients fulfilled the criteria of

TACE but refused aggressive treatment. Because of the heterogeneous nature of unresectable HCC, we conducted this case-control study. Both groups of patient were matched not only in age and tumour characteristics, but also in underlying liver function (such as serum albumin, bilirubin, prothrombin time and Child-Pugh classification). The performance status has

**Table 3.** Multivariate analysis of factors associated with longer survivals

Variables	Regression coefficient	Odds ratio (95% CI)	P-value
TACE vs. supportive	0.313	3.233 (1.751–5.972)	<0.001
Prothrombin time (INR) ≤1.2	0.459	2.771 (1.126–6.820)	0.027

CI, confidence interval; TACE, transcatheter arterial chemo-embolization; INR, international normalized ratio.

been shown to be a strong predictor of survival in patients with HCC.<sup>13</sup> In this study, the PST adopted in Barcelona Clinic Liver Cancer staging classification was used to evaluate the performance status of the patients. The concern that symptomatic patients were much more likely to refuse aggressive treatment could be excluded as the PST was matched between the two groups. The data showed that TACE could significantly prolong the median survival of up to 7 months for patients with HCC larger than 10 cm. Only two of three patients died from TACE-related complications. In our unpublished data for a series of 101 patients undergoing TACE because of HCC larger than 10 cm in diameter at the same three medical centres in Taiwan during the same periods, there were six patients (5.94%) died of TACE-related complications. The TACE-related mortality rate was comparable with 6.5% in this study. Consequently, TACE is not a harmful procedure for patients with huge HCC.

Several factors were related to the survival of HCC patients, such as tumour size, tumour stage, serum

albumin level, tumour number and vascular invasion.<sup>8–10, 14, 23</sup> In this study focusing on huge HCC, none of these factors was associated with survival in univariate and multivariate analysis. Tumour characteristic and liver reserve are the two main factors determining the survival of patients with HCC. For patients with unresectable HCCs larger than 10 cm in diameter, tumour conditions were too advanced to differentiate. Liver reserve, such as total bilirubin level and prothrombin time, was more important to influence the survival for these patients. In our previous study, CLIP score had an excellent performance to discriminate survival for patients with unresectable HCC in Taiwan.<sup>9</sup> But for patients with unresectable HCCs larger than 10 cm in diameter, the life expectancy may be too short to make the difference of survival in each tumour stage prominent. Furthermore, the case number was small and inadequate to analyse the predictive value of cancer stage.

In this study, we confirm the benefit of TACE in unresectable HCC larger than 10 cm in diameter. TACE is an independent factor significantly associated with longer survival in univariate and multivariate analysis. This finding supports the conclusion from a latest meta-analysis of 14 randomized controlled studies that TACE is beneficial for patients with unresectable HCC.<sup>17</sup>

In conclusion, the incidence of TACE-related mortality is low. For patients with unresectable HCC larger than 10 cm in diameter, TACE could be considered to provide survival benefit.

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