

## Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization and analysis of prognostic factors\*

Ming-Yuh Hsieh, Wen-Yu Chang, Liang-Yen Wang, Shinn-Cherng Chen, Wan-Long Chuang, Sheng-Nan Lu, and Ding-Kwo Wu

Department of Internal Medicine and Radiology, Kaohsiung Medical College, Kaohsiung, Taiwan, Republic of China

**Summary.** A total of 100 patients with histologically proven hepatocellular carcinoma (HCC) underwent transcatheter arterial chemoembolization (TACE) and were followed for more than 1 year and 10 months. Portal vein branch thrombosis was diagnosed in 14 patients, and extrahepatic metastasis was noted in 11 subjects. The embolization material used was iodized oil (0.1–0.2 ml/cm tumor area at its maximal diameter), which was prepared by pumping with contrast agent and then mixed with anti-cancer drugs; Gelfoam particles measuring 1–2 mm in size were subsequently injected. The overall cumulative 0.5-, 1-, 2-, and 3-year survival rates were 81%, 57%, 31%, and 21%, respectively. Patients with an intact capsule and those with solitary lesions, especially when the tumor diameter was <5 cm, achieved a higher survival rate. In contrast, incomplete TACE, extrahepatic metastasis, and portal vein thrombosis were associated with the worst outcome. Patients with positive HBsAg and diffuse or multiple tumors also showed a poor outcome. Early diagnosis and early treatment of HCC are the keys for the achievement of better clinical results.

### Introduction

Hepatocellular carcinoma (HCC) is a neoplasm that occurs worldwide [27], and it is very common in Taiwan [24]. The duration of the survival of patients with untreated HCC has been estimated to be several months at the most [4, 10, 18]. Surgical resection of HCC is an effective treatment that may prolong the survival of HCC patients [11, 12, 17].

Unfortunately, less than 10% of symptomatic HCCs are usually resectable [13]. Although using alpha-fetoprotein (AFP) and real-time sonographic screening, small HCCs can presently be detected relatively easily [21], the resectability remains low [14]. The results of various treatment modalities, including systemic [8] or intra-arterial [20] chemotherapy, immunotherapy [6], and hepatic artery ligation [16], remain unsatisfactory. Intratumor ethanol injection is effective in treating HCC, but it is suitable only for small tumors [22]. Transcatheter arterial embolization (TAE) was first reported to be effective in 1983 [29], and TAE is now accepted as the first-choice treatment for unresectable HCC. The present report describes our experience in the treatment of HCC with chemoembolization and especially concentrates on analysis of the prognostic factors.

### Patients and methods

A total of 100 patients with HCC who underwent TACE and were followed for more than 1 year and 10 months were enrolled in this study. All cases were proven to be HCC by cytology [7] and/or pathology. A total of 245 TACE treatments had been performed on these patients. Each subject received 1–10 TACE treatments during this study period.

Patients with the following conditions were not considered to be suitable candidates for embolization and were excluded from the study: (1) main portal vein thrombosis, (2) hepatofugal flow proven by angiogram, (3) a clinical performance status of Child's classification C [19] or hepatic encephalopathy, (4) prothrombin time prolonged over 3 s after vitamin K1 administration, and (5) a bilirubin level of >3 mg/dl. However, patients with portal vein branch thrombosis and extrahepatic metastasis were not excluded from the study.

The study population included 85 men and 15 women whose mean age was 54 years (range, 29–80 years). Hepatitis B surface antigen (HBsAg) was found to be positive in 77 patients. Liver cirrhosis as diagnosed by image studies and/or liver biopsy was found in 85 patients, and 20 of them were categorized as Child's classification B. An abnormal serum AFP level (>20 ng/ml) was noted in 73 subjects, 47 of whom showed a value of 400 ng/ml or greater.

Portal vein branch thrombosis as identified by sonography [1] and angiography was diagnosed in 14 patients. Extrahepatic metastasis, including lung, bone, pleural, and regional lymph-node metastases, was detected in 11 patients. For assessment of the outcome, the patients were

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Correspondence to: Ming-Yuh Hsieh, Department of Internal Medicine, Kaohsiung Medical College, 100 Shin-Chuan 1st Rd, Kaohsiung 807, Taiwan, Republic of China

**Table 1.** Cumulative survival values according to tumor type and diameter in 100 cases of HCC treated with TACE

Type	Diameter	Number of cases	Survival (%)					
			0.5 <sup>a</sup>	1.0 <sup>a</sup>	1.5 <sup>a</sup>	2.0 <sup>a</sup>	2.5 <sup>a</sup>	3.0 <sup>a</sup>
Solitary		35	100	83	69	63	52	52
	1–5 cm	11	100	91	82	82	61	61
	>5 cm	24	100	79	62	53	49	49
Multiple		54	76	50	31	16	16	7
	1–5 cm	12	100	75	50	25	25	0
	>5 cm	42	62	43	26	14	14	7
Diffuse		11	73	9	0	0	0	0
Totals		100	81	57	41	31	27	21

<sup>a</sup> Values obtained for 0.5-, 1-, 1.5-, 2-, 2.5-, and 3-year survival

**Table 2.** Univariate analysis of survival in 100 cases of HCC treated with TACE

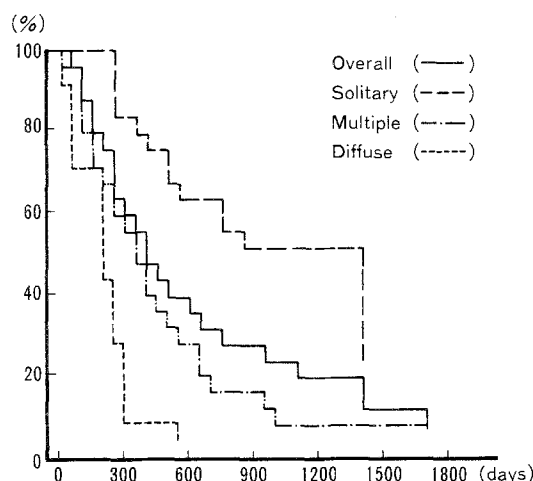
Variable	Group	Median	SE	P <sup>a</sup>
Total		424	57.0	
Sex (M/F)	M	431	65.7	0.98
	F	424	181.6	
Age (years)	<40	625	110.3	0.73
	40–59	352	58.1	
	>60	570	166.9	
Capsule	Complete	1394	19.0	<0.01
	Incomplete	308	47.3	
Type	Solitary	1394	681.7	<0.01 <sup>b</sup>
	Multiple	352	37.5	
	Diffuse	195	41.3	
Diameter (cm)	1–5	751	173.6	<0.01
	>5	352	44.4	
AFP (ng/ml)	1–20	572	133.7	0.06
	>20	367	33.6	
Portal vein	Patent	485	86.6	<0.01
	Thrombosed	342	37.4	
Metastasis	No	458	76.7	<0.01
	Yes	195	99.9	
Child's classification	Grade A	433	63.7	0.05
	Grade B	264	25.7	
HBsAg	Negative	710	54.8	0.01
	Positive	352	40.0	
TAE	Complete	649	66.3	<0.01
	Incomplete	273	24.7	
AFP decrease (%)	≥75	496	155.3	<0.01
	<75	267	27.5	

<sup>a</sup> Based on the Mantel-Cox test between Kaplan-Meier survival curves

<sup>b</sup> Tendency to be significant

categorized into three tumor types on the basis of the gross pattern: diffuse (11 patients), solitary (35 subjects), and multiple (54 patients).

TAE was usually performed immediately after diagnostic angiography [28]. Emulsified iodized oil (lipiodol) was prepared by pumping iodized oil (0.1–0.2 ml/cm<sup>2</sup> tumor area at its maximal diameter) mixed with contrast agent (at a ratio of 1:5) and an antineoplastic agent (8–10 mg mitomycin C or 30–50 mg Adriamycin) and was then slowly infused under fluoroscopy. Gelfoam particles measuring 1–2 mm in

**Fig. 1.** Cumulative survival curves generated for 100 cases of HCC treated with TACE according to tumor type

diameter and mixed with an antibiotic were subsequently cautiously injected under fluoroscopic guidance.

The factors analyzed included sex, age, tumor type, tumor size, HBsAg and AFP levels, reduction in AFP by more than 75% from the pre-TACE level, portal vein thrombosis, extrahepatic metastasis, Child's classification, TACE completeness, and capsule completeness. The latter was evaluated on the basis of various image studies, especially lipiodol CT after TACE.

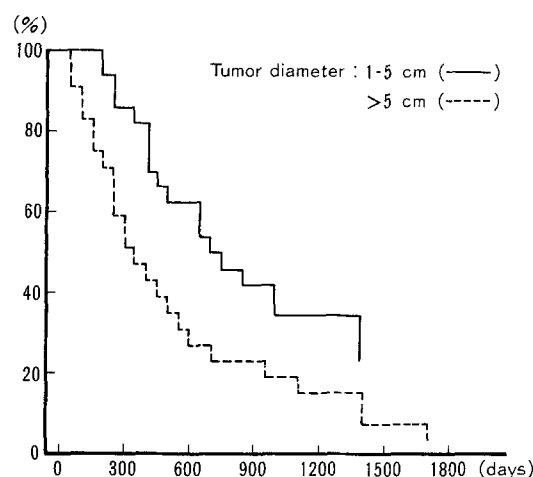
Univariate analysis was performed by computing survival curves according to the Kaplan-Meier method. Survival curves were statistically compared using the Mantel-Cox test. Variables that showed statistical significance or were close to significance in the univariate analysis were subsequently subjected to multivariate analysis using a stepwise forward version of Cox's regression procedure [2, 3] and BMDP computer software [5].

## Results

The overall cumulative 0.5-, 1-, 2-, and 3-year survival rates were 81%, 57%, 31%, and 21%, respectively (Table 1). The 3-year survival rate calculated for solitary-type HCC was 52%. The median duration of survival was 424 ± 57 days. Solitary-type HCC showed the best outcome as compared with the multiple and diffuse types of HCC. The survival period decreased significantly from the solitary type to the multiple type to the diffuse type (Table 2, Fig. 1).

Univariate survival analysis showed that sex and age were not related to the outcome (Table 2). The AFP level and Child's classification almost reached statistical significance. Patients with the following conditions had a better outcome, and the differences were statistically significant: (1) an intact capsule; (2) the solitary tumor type; (3) a tumor size of <5 cm (Fig. 2); (4) a patent portal vein; (5) the absence of extrahepatic metastasis; (6) HBsAg negativity, (7) a complete TAE, i.e., all feeding arteries including collateral vessels were completely embolized; and (8) a decrease of more than 75% in AFP levels following TACE.

When multiple possible prognostic factors were tested by Cox's hazard model, the following five appeared to be



**Fig. 2.** Cumulative survival curves generated for 100 cases of HCC treated with TACE according to tumor diameter

significantly related to survival (Table 3): (1) solitary tumor type, (2) completeness of TAE, (3) HBsAg negativity, (4) Child's classification, and (5) decrease of more than 75% in AFP levels after TACE.

The side effects encountered following TAE included fever (100%), abdominal pain (99%), vomiting (60%), GB change (19%), and alopecia (5%). All of these side effects were transient and needed only conservative treatment.

## Discussion

The prognosis for patients with untreated HCC has been reported to be extremely poor [4, 10, 18]. Surgical treatment is usually considered to be the treatment of choice for HCC, although the results remain unsatisfactory [11, 12, 17] because of coexistent cirrhosis of the liver and the large size of the tumor at the time at which patients seek medical help. Recent reports on the wide application of abdominal ultrasonography [21, 23] and AFP screening [26] have shown an increase in the early detection of HCC. However, the percentage of cases that are resectable remains low

**Table 3.** Multivariate analysis of survival in 100 cases of HCC treated with TACE

Variable <sup>a</sup>	Comparison	Odds ratio (95% CI)
Tumor type	Multiple vs solitary	2.30 (1.31 – 4.05)
	Diffuse vs solitary	5.20 (2.24 – 12.12)
Completeness of TAE	Yes vs no	0.42 (0.24 – 0.75)
HBsAg	Positive vs negative	2.13 (1.15 – 3.96)
Child's classification	Grade A vs grade B	1.99 (1.08 – 3.66)
AFP decrease	≥ 75% vs < 75%	1.78 (0.97 – 3.28)*
	Unknown vs < 75%	0.83 (0.48 – 1.44) [NS]

<sup>a</sup> The following 4 variables were not selected in the stepwise multiple logistic regression equation for lower significance level: (1) tumor diameter (≤ 5 vs > 5 cm), (2) thrombosis of portal vein branch (yes vs no), (3) initial AFP level (≤ 20 vs > 20 ng/ml), and (4) metastasis (yes vs no) AFP, Alpha-fetoprotein; CI, confidence interval; NS, not significant \*  $P = 0.06$

[14]. For patients with unresectable HCC, the results of systemic and intra-arterial chemotherapy are unsatisfactory [8, 20]. Since the report by Yamada et al. [29] that TAE is effective in treating HCC, many investigators have proven that TAE, especially TACE using lipiodol, anticancer drugs, and Gelfoam particles, exerts a remarkable antitumor effect [9, 25]. The present results are in agreement with those obtained in previous studies and thus further confirm the usefulness of TACE in the treatment of unresectable HCC.

This study was also intended to identify the factors affecting the results such that these factors could be used in the selection of patients with high potential for prolonged survival. In our univariate analysis of survival, an intact capsule, HBsAg negativity, the solitary tumor type, a small tumor diameter (< 5 cm), a patent portal vein, better reserve liver function (Child's classification A), and normal AFP levels were factors that contributed to a better outcome, and these findings were compatible with previously reported prognostic factors for surgical results [11, 15, 30]. In addition, our results showed that extrahepatic metastasis, an incomplete TACE, and the absence of a decrease of more than 75% in AFP levels following TACE were as-

**Table 4.** Correlation matrix between the significantly associated factors of univariate analysis in 100 cases of HCC treated with TACE

Variable	Significance										
1. Capsule	1										
2. TAE completeness	***	2									
3. Multiple type	***	NS	3								
4. Diffuse type	*	**	**	4							
5. Diameter	**	**	NS	NS	5						
6. Thrombosis of PV	*	**	NS	NS	*	6					
7. Child's classification	NS	NS	NS	NS	NS	*	7				
8. HBsAg	NS	NS	NS	NS	**	NS	NS	8			
9. Initial AFP	*	NS	NS	NS	NS	NS	NS	NS	9		
10. 75% AFP decrease	NS	**	NS	NS	NS	*	NS	NS	**	10	
11. Unknown AFP decrease	NS	NS	NS	NS	NS	NS	NS	NS	***	***	11
12. Tumor metastasis	*	**	*	NS	NS	NS	NS	NS	NS	NS	NS

NS, Not significant

\*  $r > 0.20$ ,  $P < 0.05$ ; \*\*  $r > 0.26$ ,  $P < 0.01$ ; \*\*\*  $r > 0.33$ ,  $P < 0.001$

sociated with a poor outcome. These results are easily understood. However, the finding that HBsAg negativity indicated a better outcome even after multivariate analysis of survival needs further clarification.

When multivariate analysis was performed using a stepwise forward version of Cox's regression procedure, only the tumor type, the completeness of TACE, HBsAg status, Child's classification, and a decrease of >75% in AFP values after TACE were independent predictors of survival. In fact, these prognostic factors usually correlate with each other to varying degrees. For example, tumor diameter (tumor size) normally correlates with capsule completeness (\*\*) and TAE completeness (\*\*), i.e., the bigger the tumor, the lower the chance for completeness of the capsule and of the TAE. However, tumor diameter did not correlate with tumor type, Child's classification, or AFP level. Interestingly, as shown in Table 4, HBsAg status correlated with tumor diameter, which means that tumors in HBsAg-positive patients were larger than those in HBsAg-negative patients in the present study. Therefore, the outcome of these two groups showed significant differences in both univariate and multivariate analyses of survival.

In conclusion, TACE was found to be effective for the treatment of HCC. Patients with an intact capsule and those with solitary-type HCC, especially when the tumor size was  $\leq 5$  cm, achieved a higher survival rate. In contrast, subjects with an incomplete TACE, extrahepatic metastasis, and portal vein invasion showed the worst outcome. Patients who were positive for HBsAg or had diffuse or multiple tumors also showed a poor outcome. Thus, early diagnosis and early treatment of HCC remain the keys for the achievement of better clinical results.

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