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Transcatheter arterial chemoembolization for hepatocellular carcinoma*

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Summary. The factors relating to the duration of survival were analyzed for 329 cases of hepatocellular carcinoma (HCC) treated by transcatheter arterial chemoembolization (TACE) between January 1, 1983, and December 31, 1990. The cumulative survival value obtained was slightly higher but not statistically significantly higher in these 329 cases as compared with the 129 cases reported in 1989. This improvement was probably attributable to careful selection of the patients on the basis of the clinical Child's status and to improvement of the superselective angiotechnique used in the present study. The overall cumulative 1-, 2-, and 3-year survival values in this series were 50%, 25%, and 15%, respectively. The median duration of survival was 12.7 months (Kaplan-Meier method). The 1-, 2-, and 3-year survival values determined for 190 patients in Child's group A, for 95 patients in Child's group B, and for 44 patients in Child's group C were 60%, 30%, and 20%; 35%, 20%, and 10%; and 35%, 20%, and 10%, respectively. Analyses were also carried out according to the tumor's type and size, the integrity of the tumor capsule, and the patency of the portal vein. Our results disclosed that a better outcome in terms of the median survival period and the survival value was favored by the following factors: a single lesion measuring less than 5 cm in diameter, an intact capsule, a patent portal vein, and a good clinical status. It is also essential that all patients who have undergone TACE be periodically evaluated by ultrasonography, CT, and angiography to determine whether repeated chemoembolization is necessary.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Taiwan and among Chinese [4]. The natural course of untreated HCC shows a poor life expectancy; the median survival period is 4 months after the onset of the initial symptoms [9]. One of the important pathological features of HCC is its tendency toward intravascular growth into both the hepatic and portal veins (PV). The incidence of main or extrahepatic portal vein thrombosis or invasion in HCC as reported for autopsy series varies from 26% to 33.8% ([1, 3, 5]; H. C. Liu, personal communication), and even higher ranges of 69%–70% are obtained when all extrahepatic and intrahepatic branches of the portal vein are also taken into account [10]. This is the main hindrance to successful chemoembolization and surgical resection. The surgical resectability of HCC is further limited by associated liver cirrhosis, which is commonly seen in our patients. Chemotherapy of HCC associated with hepatitis B, via either an intravenous or an intraarterial route, has been disappointing and of limited efficacy [2, 6, 7, 11, 12, 17].

Chemoembolization has recently become the treatment of choice in cases of unresectable HCC. A total of 329 patients with HCC were given 654 courses of chemoembolization in our hospital between January 1983 and December 1990. In 1989, we reported the results of TACE for the first 129 cases of unresectable HCC, and the duration of survival and the outcome of these patients were closely related to a good clinical status, to a patent PV, and to the integrity of the tumor capsule [16]. Besides analyzing the aforementioned factors, the present report also provides a further evaluation of the correlation of the size and type of the tumors with the patients' outcome.

Patients and methods

Between January 1983 and December 1990, 329 patients with HCC were diagnosed and treated with 654 courses of TACE. The study population included 303 men and 26 women whose ages ranged from 21 to 80 years.

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Table 1. Analysis of the survival of 329 patients with HCC who received a total of 654 TACE treatments, based on Child's status, patency of the portal vein, tumor capsule integrity, tumor size, and tumor type

		Number of cases	Median survival period[a]	Survival		
				1-year	2-year	3-year
Cumulative		329	12.7 months	50%	25%	15%
Child's status*	A	190	14.5 months	60%	30%	20%
	B	95	8.0 months	35%	20%	10%
	C	44	7.5 months	35%	20%	10%
PV*:						
	Intact	66	24.1 months	85%	45%	40%
	Branch	246	14.6 months	60%	25%	15%
	Main	17	7.5 months	45%	10%	5%
Capsule*:						
	Intact	50	29.4 months	90%	58%	45%
	Broken	110	12.2 months	50%	15%	10%
	No capsule	169	9.1 months	38%	10%	5%
Size*:						
	≦5 cm	71	20.5 months	75%	40%	25%
	>5 to ≦10 cm	74	15.8 months	65%	30%	20%
	>10 cm	184	9.1 months	45%	15%	10%
Type*:						
	Single	25	17.4 months	70%	40%	40%
	Multiple	248	13.8 months	60%	25%	20%
	Diffuse	56	4.5 months	25%	0	

[a] Kaplan-Meier method
$P = 0.0001$
* Child's classification

All cases were considered to be unresectable because of multiple lesions over both lobes of the liver and severe coexistent liver cirrhosis. Prior to TACE, hepatic arteriography was performed to obtain information about the size, type, location, and feeding arteries of the tumor. The PV should be viewed in the late venous phase to evaluate the degree of PV invasion.

An anticancer agent was mixed with lipiodol (<15 ml), and the mixture was then infused slowly into the feeding hepatic artery via a catheter. Gelfoam strips cut into 1- to 2-mm pieces were soaked in water-soluble contrast medium and infused until complete arrest of the tumor arterial blood flow was achieved. The anticancer drugs used were mitomycin C, Adriamycin, and epirubicin.

Liver function was evaluated prior to and after TACE. Periodic follow-up study by ultrasonography, CT, and angiography was necessary to determine whether further TACE would be required. We used the Kaplan-Meier method for survival analysis based on the clinical status (Child's classification A, B, and C), the patency of the portal vein, the integrity of the tumor capsule, and the tumor's size and type.

Results

The cumulative survival values were 50.0% at 1 year, 25.0% at 2 years, and 15.0% at 3 years. The median duration of survival was 12.7 months (Kaplan-Meier product-limit method). The survival values determined for 190 patients in the Child's A group, for 95 subjects in the Child's B group, and for 44 patients in the Child's C group were 60%, 35%, and 35% at 1 year; 30%, 20%, and 20% at 2 years; and 20%, 10% and 10% at 3 years, respectively, and the median duration of survival was 14.5, 8.0, and 7.5 months, respectively. The differences in survival as a function of the clinical status (Child's classification A, B, and C) were statistically significant (Kaplan-Meier method, $P = 0.0001$).

The survival values calculated for 66 patients with an intact portal vein, for 246 subjects with branch invasion, and for 17 patients with main portal vein invasion were 85%, 60%, and 45% at 1 year; 45%, 25%, and 10% at 2 years; and 40%, 15%, and 5% at 3 years, respectively, and the median duration of survival was 24.1, 14.6, and 7.5 months, respectively. The differences in survival as a function of portal vein invasion were statistically significant (Kaplan-Meier method, $P = 0.0001$).

The differences in the survival of 50 patients with an intact capsule, of 110 subjects with a broken capsule, and of 169 patients with no capsule were statistically significant (Kaplan-Meier method, $P = 0.0001$). The respective survival values determined for these subjects were 90%, 50%, and 38% at 1 year; 58%, 15%, and 10% at 2 years; and 45%, 10%, and 5% at 3 years, and the median duration of survival was 29.4, 12.2, and 9.1 months, respectively.

The differences in the survival of 71 patients with a tumor measuring less than 5 cm in diameter of 74 subjects with a lesion measuring between 5 and 10 cm in diameter, and of 184 patients with a tumor measuring more than 10 cm in diameter were statistically significant (Kaplan-Meier method, $P = 0.0001$). The respective survival values calculated for these patients were 75%, 65%, and 45% at 1 year; 40%, 30%, and 15% at 2 years; and 25%, 20%, and 10% at 3 years, and the median duration of survival was 20.5, 15.8, and 9.1 months, respectively.

The median duration of survival for 25 patients with a single tumor, for 248 subjects with multiple tumors, and for 56 patients with diffuse-type tumors was 17.4, 13.8, and 4.5 months, respectively, and these differences were statistically significant (Kaplan-Meier method,

Table 2. Complications in 26 patients who underwent a total of 654 TAE procedures

Mortality within 1 month	Number of cases	Morbidity	Number of cases
Hepatic failure	8	Acute renal failure	2
Tumor rupture	2	Transient azotemia	1
EV rupture	2	Hepatorenal syndrome	1
GB rupture	1	Cholecystitis	3
Septic shock	1	Liver abscess	3
Respiratory failure	1	Transient paraplegia	1
Total	15	Total	11

$P = 0.0001$). The respective survival values determined for these patients were 70%, 60%, and 25% at 1 year and 40%, 25%, and 0 at 2 years. The diffuse type was the worst prognostic sign, with all 56 patients dying within 1 year (Table 1).

The overall complication rate was 3.9% for a total of 654 TAE procedures; the most common complication was hepatic failure inducing mortality within 1 month (Table 2).

Discussion

The high correlation of hepatitis-B carrier and cirrhosis in HCC patients has been well established [14]. Determination of the serum α-feto-protein level and ultrasonography have also been used to detect small HCC early and thus improve the surgical resectability [8, 13, 14]. However, the surgical resectability of HCC patients presenting at our institution has remained unchanged because most HCC cases remain asymptomatic as long as the tumor is small and because of the fast-growing, aggressive character of HCC, which causes this disease to reach an advanced stage before the patient seeks medical help. The results of both intra-arterial and intravenous chemotherapy have been unsatisfactory, and TACE remains the only choice of treatment when tumors are surgically unresectable [2, 6, 7, 11, 12, 17].

The results obtained in the current series of 329 patients are slightly better, albeit not statistically significantly so (Kaplan-Meier method, $P = 0.0001$), than our previously reported findings [16]. The present results showed significant differences in the survival values determined for patients between Child's groups A and B, between those displaying PV patency and those showing PV invasion, and between those exhibiting an intact capsule versus a broken capsule versus no capsule at all. In addition, the tumor size (i.e., less than 5 cm, between 5 and 10 cm, and larger than 10 cm) and the tumor type (i.e., single, multiple, diffuse tumor) also influenced the patients' survival.

It is our belief that careful selection of patients with a single, small tumor (less than 5 cm in diameter); a good clinical status; an intact PV; and an intact capsule would result in an improvement in the survival of patients treated by TACE. Further studies are needed to establish new treatment methods using new combinations of anticancer agents to improve the prognosis for patients with advanced HCC [15].

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