Influence of Transcatheter Arterial Chemoembolization on the Prognosis after Hepatectomy for Hepatocellular Carcinoma in Patients with Severe Liver Dysfunction

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Abstract. *Background: The influence of preoperative transcatheter arterial chemoembolization (TACE) on postoperative survival and recurrence of hepatocellular carcinoma (HCC) after resection is still controversial. The effect of preoperative TACE on the prognosis of HCC after hepatectomy in 243 patients with liver dysfunction was evaluated. Materials and Methods: Among 243 patients who underwent curative resection of HCC between 1992 and 2005, 124 patients had an indocyanine-green retention rate at 15 min (ICGR15) of <17% (49 underwent TACE), while 119 patients had an ICGR15 of ≥17% (66 underwent TACE). The clinical characteristics, operative results and long-term survival were compared between patients with and without preoperative TACE who had mild or severe liver dysfunction. Results: There was no significant difference in the recurrence-free and overall survival rates between the TACE and no TACE groups with an ICGR15 <17%. Among the 119 patients with an ICGR15 ≥17%, there were no significant differences of preoperative characteristics, operative findings, or histology between the two groups. However, the post-resection disease-free and overall survival rates of 66 patients who underwent TACE were significantly better than those of 53 patients who did not have TACE (p=0.009 and p=0.0099, respectively). Using multivariate analysis, preoperative TACE was independently associated with better disease-free and overall survival after resection in patients with an ICGR15 ≥17% (p=0.0309 and p=0.0162, respectively). Conclusion: Preoperative TACE did not alter the prognosis after resection of HCC in patients with mild liver dysfunction, but it did improve the prognosis of patients with severe liver dysfunction.*

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Advances in surgical techniques and perioperative management have transformed resection of hepatocellular carcinoma (HCC) into a relatively safe operation with a low mortality rate (1). However, long-term survival is still unsatisfactory because of the high recurrence rate after curative resection (2). Macroscopic or microscopic portal vein involvement and intrahepatic metastasis are the factors that are most consistently reported to be associated with a poor prognosis after surgery (3, 4). Development of new tumors in the remnant liver, *i.e.*, *de novo* primary HCC, may also affect survival (5). In order to achieve a better prognosis, it is important to prevent recurrence after initial resection of HCC, but there is currently no standard therapy for intrahepatic metastasis.

With the development of interventional radiology, transcatheter arterial chemoembolization (TACE) has become an increasingly important palliative treatment for HCC. Initially, TACE was only performed to treat unresectable HCC, as well as some early tumors that were extremely difficult to resect. More recently, TACE has been used as preoperative adjuvant therapy for resectable HCC with the hope that it may improve survival (6-11). Based on the currently available evidence, however, preoperative TACE is not routinely recommended in patients undergoing hepatectomy for resectable HCC (12-14), and TACE may be contraindicated in patients with cirrhosis, because it can cause progressive deteroration of liver function (12). Whether preoperative TACE is effective for improving the long-term survival of HCC patients is still controversial, and there have been few reports about the long-term outcome after curative resection of HCC in patients receiving preoperative TACE who were stratified according to liver function.

The aim of this study was to compare the effect of preoperative TACE on long-term disease-free survival and

overall survival in patients with or without severe liver dysfunction who underwent resection of HCC. We also investigated the important prognostic indicators for recurrence and survival after resection of HCC in patients with severe liver dysfunction.

Materials and Methods

Patients. Between February 1992 and February 2005, 245 patients with HCC underwent curative hepatectomy at our institution and were classified into two groups with a preoperative indocyanine-green retention rate at 15 min (ICGR15) of <17% or ≥17%. An ICGR15 of 17% was the median preoperative value in all 245 patients. Of the 124 patients with an ICGR15 <17%, TACE was performed preoperatively in 49. Among the 119 patients with an ICGR15 ≥17%, TACE was performed in 66. All patients gave informed consent to their treatment.

Chemoembolization. TACE was first performed at our hospital in 1983 as preoperative adjuvant therapy for resectable HCC. Although this study was not a prospective randomized trial, the allocation of preoperative TACE was determined randomly rather than selectively. In part, it was selected according to the patients' desires, provided that their liver function met the criteria of Child A or B and there were no tumor thrombi in the portal trunks.

During the study period, the procedure was as follows: A catheter was selectively inserted into the right or left hepatic artery, a segmental artery, or a subsegmental artery using the Seldinger method. Embolic materials included Gelfoam particles and iodized oil (Lipiodol), with the Lipiodol (mean dose ±SD: 3.9±2.5 ml) being mixed with an anticancer drug to form an emulsion before injection. The anticancer drugs used included epirubicin (Farmorubicin) (mean dose: 48.2±16.5 mg). Among 49 patients with an ICGR15 <17%, TACE was performed *via* the right hepatic artery in 24 patients, the left hepatic artery in 12 patients, a segmental artery in 8 patients, and a subsegmental artery in 5 patients. Among 66 patients with an ICGR15 ≥17%, TACE was performed *via* the right hepatic artery in 16 patients, the left hepatic artery in 9 patients, a segmental artery in 13 patients, and a subsegmental artery in 28 patients.

Clinicopathologic variables and operative procedures. Before surgery was performed after TACE, each patient underwent ICGR15 measurement, technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin liver scintigraphy and conventional liver function tests. Hepatitis screening was done by measurement of hepatitis B surface antigen and hepatitis C antibody, while α-fetoprotein (AFP) and protein induced by vitamin K absence/antagonism (PIVKA)-II were also measured in all patients.

Our operative procedures have been reported previously (15, 16). The method of hepatectomy was largely chosen according to the criteria of Makuuchi *et al.* (17, 18), and the procedures were classified according to conventional terminology with respect to the eight liver subsegments of Couinaud (19). Anatomic resection was defined as lobectomy (resection of one liver lobe), extended lobectomy (lobectomy plus removal of additional contiguous segments), or segmentectomy (resection of two Couinaud subsegments). All of the other non-anatomic procedures were classified as limited resection. One senior pathologist reviewed each specimen for histological confirmation of the diagnosis. Tumor size was recorded as the maximum diameter and the resection margin width was measured as the distance from the tumor edge to the resection line. Tumor necrosis was classified into three grades: complete necrosis (only necrotic tissue and no viable tumor cells), partial necrosis (both viable and necrotic tumor cells), or no necrosis.

Follow-up. All patients were followed up at our outpatient clinics after discharge. Routine imaging studies, such as ultrasonography, computed tomography, or magnetic resonance imaging, were performed every 2-3 months in addition to measurement of the serum AFP and PIVKA-II levels. When recurrence was detected on the basis of an increase in tumor marker levels and/or by imaging, patients who had recurrence limited to the remnant liver were treated by TACE, lipiodolization, repeat resection, or ablation therapy, such as percutaneous radiofrequency therapy.

Prognostic factors. We used univariate and multivariate analysis of 25 clinicopathological factors to identify independent variables closely related to disease-free and overall survival after resection in HCC patients with an ICGR15 ≥17% (Tables II and III). The patient factors studied were gender, age, hepatitis C virus infection, hepatitis B virus infection, alcohol abuse, liver function (including albumin, total bilirubin, transaminases, prothrombin time, platelet count, technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin liver scintigraphy, and Child-Pugh classification), and performance of preoperative TACE. The tumor factors studied were AFP, PIVKA-II, histological features (including maximum tumor diameter), number of tumors, differentiation, microscopic capsule formation, microscopic invasion of the portal and/or hepatic veins, grade of fibrosis, and tumor stage as defined with the TNM classification (20). The operative factor studied was the need for perioperative blood transfusion. All variables that were significant according to univariate analysis were subsequently examined using a Cox's proportional hazards model to identify independent predictors of disease-free survival and/or overall survival after hepatic resection.

Statistical analysis. Continuous variables are presented as the mean±standard deviation (SD). The significance of differences between two groups was assessed using the Chi-squared test or the unpaired Student's *t*-test as appropriate. The Kaplan-Meier life-table method was used to calculate disease-free and overall survival rates as of June 2005. Differences of survival were estimated using the generalized log-rank test for univariate analysis, while the stepwise Cox regression method was used for multivariate analysis. For all analyses, $p<0.05$ was considered statistically significant.

Results

Clinical characteristics, disease-free survival and overall survival of patients with an ICGR15 <17%. Table I shows the perioperative characteristics of the HCC patients with ICGR15 <17%. There were no significant differences between the groups with and without preoperative TACE, including their background characteristics, preoperative laboratory data, surgical procedures, intraoperative findings,

Table I. *Perioperative characteristics of the patients with and without preoperative TACE*

	ICGR15<17%			ICGR15≥17%		
	TACE (+)	TACE (–)	*p*-value	TACE (+)	TACE (–)	*p*-value
No.	49	75		66	53	
Gender (male/female)	40/9	62/13	0.8829	46/20	43/10	0.1533
Age (years)	61.9±12.0	63.0±8.9	0.5614	65.6±8.0	65.1±7.7	0.6907
HCV (+/–)	26/23	51/24	0.0937	49/17	44/9	0.2495
HBV (+/–)	9/40	15/60	0.8220	7/59	1/52	0.0591
Alcohol abuse (+/–)	21/28	32/43	0.9833	22/44	26/27	0.0823
Preoperative laboratory data (mean±SD)						
Platelet count (10^4/μl)	17.5±8.7	15.5±6.2	0.1632	10.9±5.3	11.6±4.4	0.4038
Total bilirubin (mg/dl)	0.73±0.28	0.75±0.27	0.8031	0.99±0.35	0.94±0.32	0.4260
Albumin (g/dl)	3.87±0.34	3.97±0.31	0.1039	3.50±0.37	3.62±0.32	0.0710
AST (IU/l)	37±14	45±27	0.0632	61±35	60±30	0.8636
ALT (IU/l)	44±28	55±40	0.0921	54±39	62±40	0.2715
Prothrombin time (%)	93±10	95±10	0.2555	82±12	84±10	0.1857
GSA Rmax (mg/min)	0.595±0.211	0.534±0.170	0.1164	0.336±0.161	0.368±0.156	0.3368
ICGR15 (%)	11.1±3.1	11.5±3.3	0.4543	26.5±6.7	24.4±6.4	0.1056
Child-Pugh class (A/B/C)	46/3/0	74/1/0	0.1400	52/14/0	48/5/0	0.0813
AFP (ng/ml)	1471±6388	1633±8585	0.9105	95±167	224±628	0.1144
PIVKA II (mAU/ml)	1082±5130	1897±7845	0.5423	753±4451	887±2114	0.8448
Operative procedure (anatomic/limited)	13/36	23/52	0.6199	6/60	11/42	0.0707
Operative blood loss (ml) (mean±SD)	1048±839	1237±1895	0.5120	1325±1085	1163±1265	0.4513
Blood transfusion (+/–)	18/31	31/44	0.6086	30/36	18/35	0.2040
Tumor size (cm) (mean±SD)	4.07±2.44	3.94±3.40	0.8209	3.21±1.61	3.03±1.75	0.5535
Number of tumors (solitary/multiple)	45/4	59/16	0.0513	58/8	44/9	0.4515
Histology (Well/Moderately/Poorly)	6/33/1	15/54/4	0.5514	7/35/2	13/34/1	0.4417
fc (+/–)	47/1	68/7	0.1117	59/4	45/7	0.1968
VP and/or VV (+/–)	19/27	36/36	0.3557	18/37	18/32	0.8928
TW (+/–)	0/49	3/72	0.1564	3/63	0/53	0.1159
im (+/–)	3/46	5/70	0.9040	1/65	3/50	0.2124
Associated liver disease (normal/fibrosis or hepatitis/cirrhosis)	8/28/12	14/42/19	0.9537	1/25/38	6/18/28	0.0805
Tumor stage (I/II/III/IV)	26/22/1/0	34/37/4/0	0.5259	38/24/4	27/24/2	0.5708
Necrosis (complete/partial/none)	14/31/4*	–		32/33/1	–	

The chi-square test or the unpaired Student's t-test was used for statistical analysis. *$p<0.05$ *vs.* ICGR15 ≥17% with TACE.
ICGR15, indocyanine green retention rate at 15 minutes; HCV, hepatitis C virus; HBV, hepatitis B virus; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GSA Rmax, maximum removal rate of technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin; ICGR15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonism-II; fc, microscopic capsule formation; VP, microscopic portal vein invasion; VV, microscopic hepatic vein invasion; im, microscopic intrahepatic metastases; TW, microscopic margin <5 mm from the tumor border; im, microscopic intrahepatic metastases.

and histological features of the resected specimens. Complete necrosis of the resected tumors was confirmed by histological examination in 14 out of the 49 patients (28%) who underwent TACE. The disease-free survival rates and overall survival rates of the patients with and without preoperative TACE are compared in Figures 1 and 2. The disease-free survival rates of patients with and without TACE were 60.4% and 58.9% at 3 years, 38.8% and 38.7% at 5 years and 31.1% and 34.8% at 7 years, respectively. Overall survival rates of the patients with and without TACE were 87.9% and 85.6% at 3 years, 83.3% and 73.6% at 5 years and 61.7% and 52.3% at 7 years, respectively. There were no significant differences in disease-free survival ($p=0.8817$) or overall survival ($p=0.3581$) between the patients with and without TACE.

Clinical characteristics, disease-free survival, and overall survival of patients with an ICGR15 ≥17%. Among the patients with an ICGR15 ≥17%, there were no differences of perioperative characteristics between 66 patients who received preoperative TACE and 53 patients who did not (Table I). However, the disease-free survival rate of the patients undergoing TACE was significantly higher than that of those who did not receive it (Figure 3), with the respective rates being 70.2% *versus* 31.3% at 3 years, 47.1% *versus* 12.5% at 5 years and 40.4% *versus* 12.5% at 7 years ($p=0.009$). Preoperative TACE, an

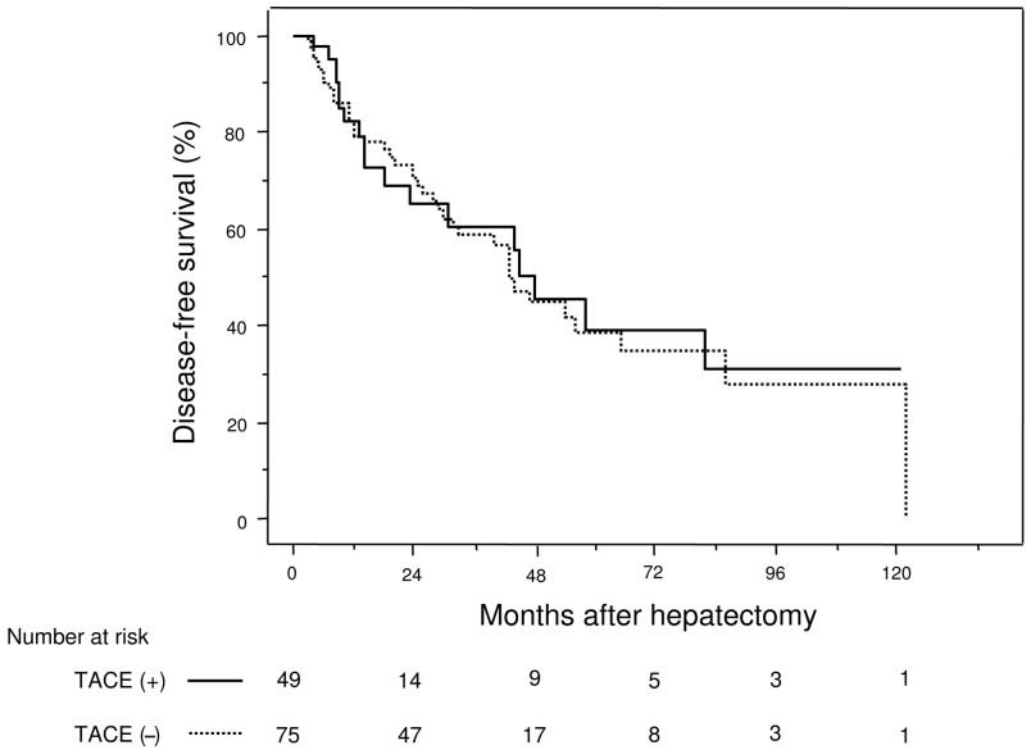

Figure 1. *Disease-free survival after hepatectomy for hepatocellular carcinoma in patients who had an ICGR15 <17% with and without preoperative TACE (p=0.8817). Unbroken line: patients with TACE. Dotted line: patients without TACE. The number of patients at risk is shown below the graph.*

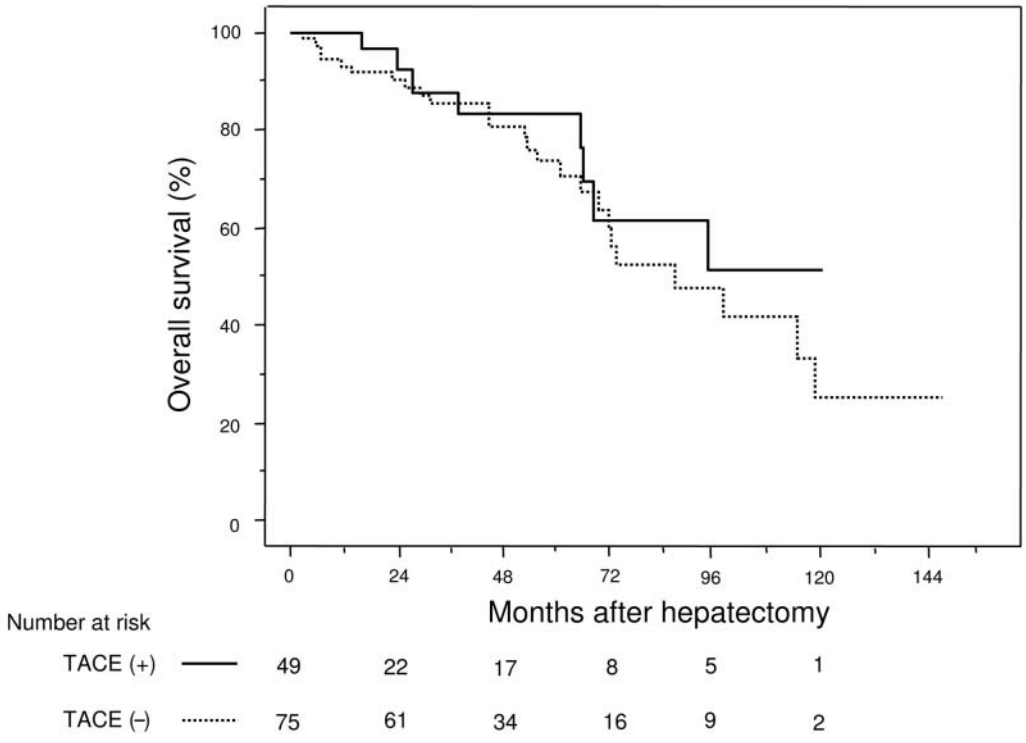

Figure 2. *Overall survival after hepatectomy for hepatocellular carcinoma in patients with who had an ICGR15 <17% with and without preoperative TACE (p=0.3581). Unbroken line: patients with TACE. Dotted line: patients without TACE. The number of patients at risk is shown below the graph.*

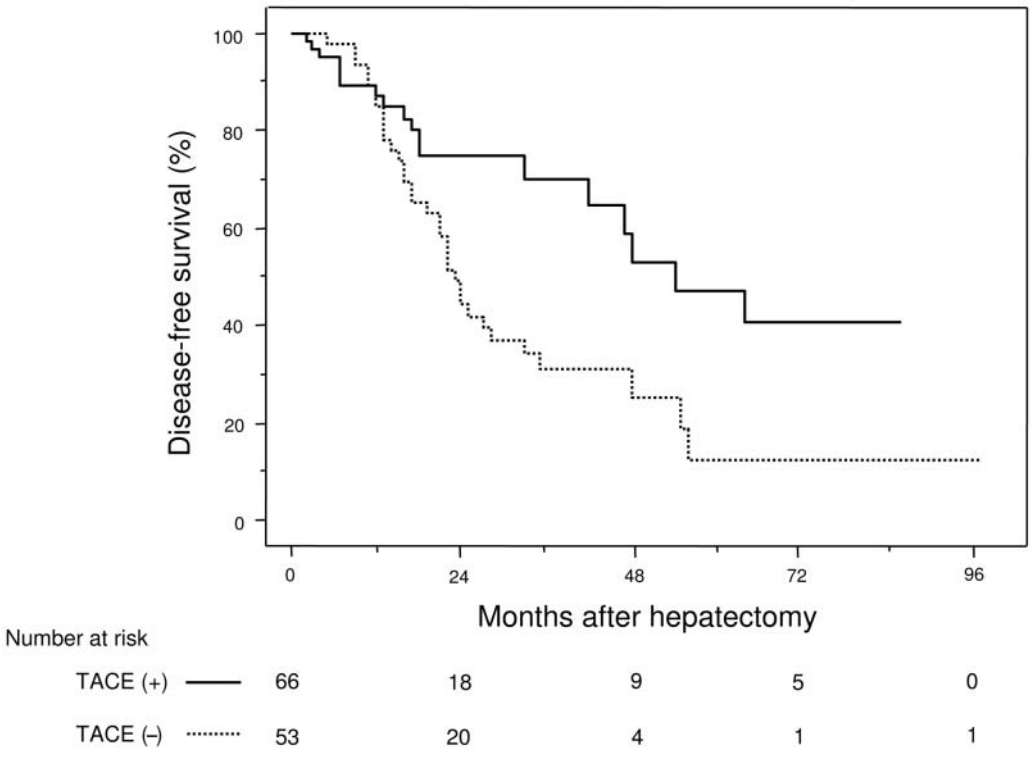

Figure 3. *Disease-free survival after hepatectomy for hepatocellular carcinoma in patients who had an ICGR15 ≥17% with and without preoperative TACE (p=0.009). Unbroken line: patients with TACE. Dotted line: patients without TACE. The number of patients at risk is shown below the graph.*

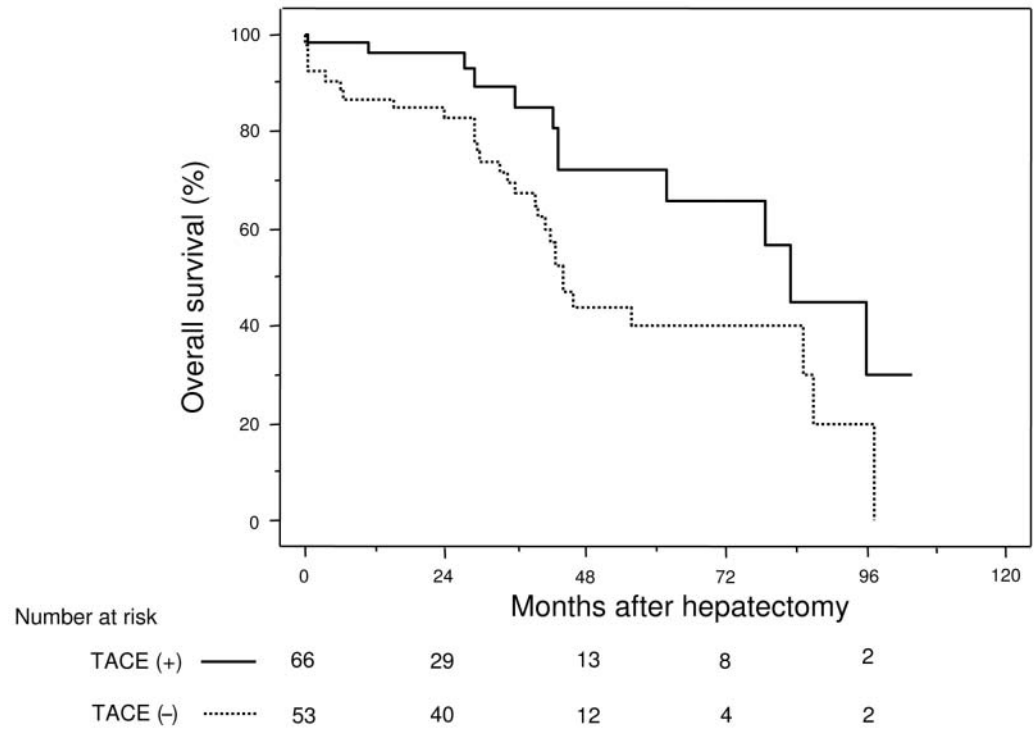

Figure 4. *Overall survival after hepatectomy for hepatocellular carcinoma in patients who had an ICGR15 ≥17% with and without preoperative TACE (p=0.0099). Unbroken line: patients with TACE. Dotted line: patients without TACE. The number of patients at risk is shown below the graph.*

Table II. *Univariate analysis of factors potentially affecting disease-free and overall survival after hepatectomy in HCC patients with an ICGR15 ≥17%.*

Variable		*p*-value	
		Disease-free survival	Overall survival
Gender	(male *vs.* female)	0.8384	0.6075
Age (years)	(<67 *vs.* ≥67)	**0.0004**	**0.0265**
HCV	(No *vs.* yes)	0.1212	0.2037
HBV	(No *vs.* yes)	0.2796	0.5003
Alcohol abuse	(No *vs.* yes)	0.7731	0.6458
Platelet count (/mm^3)	(<110.000 *vs.* ≥110.000)	0.6371	0.3383
Total bilirubin (mg/dl)	(<0.9 *vs.* ≥0.9)	**0.0141**	**0.0077**
Albumin (g/dl)	(<3.6 *vs.* ≥3.6)	0.0633	0.3487
AST (IU/dl)	(<55 *vs.* ≥55)	**0.0217**	0.7707
ALT (IU/dl)	(<47 *vs.* ≥47)	0.1256	0.8048
Prothrombin time (%)	(<82 *vs.* ≥82)	**0.0288**	0.6135
GSA Rmax (mg/min)	(<0.333 *vs.* ≥0.333)	0.8501	0.1690
Child-Pugh class	(class A *vs.* B)	0.6909	0.1790
AFP (ng/ml)	(< 22 *vs.* ≥ 22)	0.4858	0.0759
PIVKA II (mAU/ml)	(< 36 *vs.* ≥ 36)	**0.0464**	0.2528
Preoperative TACE	(no *vs.* yes)	**0.0090**	**0.0099**
Operative procedure	(anatomic *vs.* limited)	0.4844	0.7515
Blood transfusion	(no *vs.* yes)	0.5682	0.5959
Tumor size (cm)	(<2.8 *vs.* ≥2.8)	0.3450	0.5259
Number of tumors	(solitary *vs.* multiple)	**0.0033**	0.3183
Histology	(well/moderately *vs.* poorly)	0.1851	0.9532
fc	(no *vs.* yes)	0.1307	**0.0405**
VP and/or VV	(no *vs.* yes)	0.4801	**0.0420**
Associated liver disease normal *vs.* fibrosis *vs.* cirrhosis		0.4004	0.6018
Tumor stage	(I *vs.* II *vs.* III)	0.4697	0.1164

The Kaplan-Meier life table method was used to calculate the disease-free and overall survival rates; differences of survival were estimated using the generalized log-rank test.
HCV, hepatitis C virus; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GSA Rmax, maximum removal rate of technetium-99m-diethylenetriamine pentaacetic acid-galactosyl human serum albumin; AFP, a-fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonism-II; TACE, transcatheter arterial chemoembolization; fc, microscopic capsule formation; VP, microscopic portal vein invasion; VV, microscopic hepatic vein invasion; im, microscopic intrahepatic metastases.

Table III. *Prognostic factors for disease-free survival and overall survival identified by multivariate analysis in HCC patients with an ICGR15 ≥17%.*

Variable	Coefficient	SE	Relative risk	*p*-value
Disease-free survival:				
Preoperative TACE (+)	–0.656	0.304	0.519	0.0309
Age ≥67 years	1.455	0.331	4.292	<0.0001
Total bilirubin ≥0.9 mg/dl	1.146	0.313	3.145	0.0002
Multiple tumors	1.141	0.388	3.125	0.0033
Overall survival:				
Preoperative TACE (+)	–0.892	0.371	0.410	0.0162
Age ≥67 years	1.268	0.380	3.559	0.0009
Total bilirubin ≥0.9 mg/dl	1.237	0.394	3.448	0.0017
VP and/or VV (+)	0.943	0.359	2.571	0.0087

TACE, transcatheter arterial chemoembolization; VP, microscopic portal vein invasion; VV, microscopic hepatic vein invasion; SE, standard error.

age ≥67 years, a total bilirubin level ≥0.9 mg/dl, and multiple tumors were found to be factors with a significant influence on disease-free survival according to both univariate and multivariate analyses (Tables II and III). A significant influence on overall survival was also observed (Figure 4), with the respective survival rates with and without TACE being 85.2% *versus* 67.1% at 3 years, 72.4% *versus* 39.9% at 5 years and 45.2% *versus* 39.9% at 7 years ($p=0.0099$), respectively. Preoperative TACE, age ≥67 years, total bilirubin ≥0.9 mg/dl, and microscopic portal vein invasion (vp) and/or hepatic vein invasion (vv) were significant determinants of overall survival according to both univariate and multivariate analyses (Tables II and III).

Complete necrosis of the resected tumors was comfirmed by histological examination in 32 out of 66 patients (48%) who underwent TACE, and there was a significantly higher incidence of complete necrosis in patients with an ICGR15 ≥17% than those with an ICGR15 <17% (Table I). Subsegmental TACE was performed in only 5 out of 49 patients (10%) with an ICGR15 <17% *versus* 28 out of 66 patients (42%) with ICGR15 ≥17%, a difference that was statistically significant ($p<0.03$). There were no complications of TACE that required delay or discontinuation of surgery.

Discussion

TACE is recognized as a treatment for HCC, either as adjuvant therapy to resection or as a definitive procedure in patients with tumors that are considered to be unresectable (21, 22). The purpose of preoperative TACE is not only to prevent recurrence by controlling intrahepatic spread *via* the portal system, but also to facilitate surgery by reducing tumor bulk. In particular, decreasing resection of non-tumorous liver is vital to avoid postoperative hepatic failure in patients with cirrhosis. Uchida *et al.* (12) reported a lower survival rate of patients with cirrhosis who underwent TACE prior to resection of HCC compared with patients who did not. They, therefore, recommended against the preoperative performance of TACE, because the procedure itself may accelerate deterioration of compromised liver function, particularly in patients with cirrhosis. Lu *et al.* (9) performed a retrospective analysis of 120 HCC patients and concluded that preoperative TACE might benefit those with tumors >8 cm in diameter, but not those with tumors

measuring 2-8 cm. In contrast, it was reported that downstaging or total necrosis of the tumor was induced by preoperative TACE in 62% of 103 HCC patients with cirrhosis, leading to improved disease-free survival after both liver resection and transplantation (11). Thus, the value of preoperative TACE is still controversial.

We compared the long-term prognosis after resection of HCC in patients with and without preoperative TACE who were classified into groups with mild or severe liver dysfunction. Although we found that preoperative TACE was not associated with better disease-free or overall survival among patients with an ICGR15 <17%, it did improve the prognosis of patients with an ICGR15 ≥17%. We also found that preoperative TACE was an independent factor associated with a better prognosis in HCC patients with severe liver dysfunction. Some authors (11, 23) have graded the efficacy of preoperative TACE with reference to the extent of tissue necrosis on examination of resected specimens. Adachi *et al.* (23) reported a higher disease-free survival rate after TACE achieved complete tumor, necrosis, while there was an increased incidence of recurrence when only partial necrosis occurred. Matsui *et al.* (24) reported that subsegmental TACE was technically successful in about 80% of patients with small HCCs, while complete necrosis could be achieved in about 70% of hypervascular HCCs less than 4 cm in diameter by one subsegmental procedure. Accordingly, TACE is not only useful for large tumors, but can also eliminate small lesions and can cause necrosis of daughter nodules. We routinely perform subsegmental TACE in HCC patients with cirrhosis to achieve an antitumor effect and suppress further deterioration of the residual hepatic parenchyma. In this study, the number of subsegmental TACE procedures performed in HCC patients with an ICGR15 ≥17% was significantly greater than in those with an ICGR15 <17%. We suggest that complete tumor necrosis was significantly more common in patients with an ICGR15 ≥17%, probably as a result of using subsegmental TACE and treating smaller tumors. Our data indicate that preoperative TACE is effective in patients with severe liver damage if it achieves complete tumor necrosis.

In conclusion, preoperative TACE is effective for reducing the incidence of postoperative recurrence and for prolonging survival in patients with resectable HCC and severe liver dysfunction. Further prospective studies will be required to fully evaluate the utility of preoperative TACE in patients with potentially curable HCC.

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