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Treatment Outcome of Transcatheter Arterial Chemoinfusion According to Anticancer Agents and Prognostic Factors in Patients with Advanced Hepatocellular Carcinoma (TNM Stage IVa)

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Transcatheter arterial chemoinfusion (TACI) is the main treatment modality for advanced hepatocellular carcinoma (HCC). However, the therapeutic efficacy of TACI according to anti-cancer agents and prognostic factors for advanced HCC (TNM stage IVa) has not been previously clarified. A total of 127 patients with TNM stage IVa HCC were divided into intra-arterial Adriamycin (Group I) and intra-arterial Cisplatin (Group II) infused groups, according to the anticancer agents that were used. We compared the therapeutic efficacy of TACI applied anticancer agents, and we also analyzed the prognostic factors which influenced the survival rates. Chi-square test, t-test, Cox's proportional hazard regression model, and Kaplan-Meier method were performed. The overall survival was significantly different (10.0 vs 5.7 months, respectively) and the results favored Group I. On univariate analysis, the significant prognostic factors included age, portal vein thrombosis (PVT), tumor size (diameter > 5 cm), type of tumor, the reduction rate (tumor size & alpha- fetoprotein) after 3 months of chemotherapy, serum albumin level, serum alkaline phosphatase level and total serum bilirubin levels at the time of diagnosis. After repeated chemotherapy, Group I showed better survival (14.0 vs 7.9 months). However, there was no statistical difference in the survival rate of the two groups for cases involving large tumors, PVT and diffuse type of HCC. Group I showed better survival than Group II. However, when the other prognostic factors were taken into consideration, there was no significant difference in the survival rate of the two groups, except for the cases with small or nodular HCC.

Key Words: Hepatocellular carcinoma, transcatheter arterial chemoinfusion, treatment outcome, prognostic factors

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Hepatocellular carcinoma (HCC) in Korea is one of the most prevalent malignant tumors and it has a high mortality rate. Because the prognosis is extremely poor, the majority of patients with advanced HCC live no longer than 6 months from the day of the initial diagnosis. Surgical resection is generally accepted as the first choice of treatment for HCC. However, due to its multifocal nature, its association with chronic liver diseases and frequent postresectional recurrence, surgery is not possible for most patients at the time of diagnosis.[1-4] No other effective treatment is currently known. At present, for those patients with advanced HCC, transcatheter arterial chemoinfusion (TACI) is the main treatment modality.[5-7] Various anticancer agents have been used for TACI. However, it is difficult to interpret the therapeutic efficacy of these agents because HCC stage, hepatic function and other prognostic factors need to be quantified. In addition, there have been recent reports to the effect that TACI does not improve survival rates and this places emphasis upon the need for an accurate assessment of therapeutic efficacy.[8-10]

Prospective studies are limited since it is hard to compare patients with equivalent conditions,

with respect to the degree of the tumor progression and the health status of patients, and in particular the hepatic function. Even in the case of a TNM stage IVa classification[11] representing an advanced HCC, there could be differences in terms of the anatomical morphology of the tumor and the presence of portal vein thrombosis (PVT) (Fig. 1). Therapeutic efficacy and prognosis could vary due to these differences, and the analysis of these factors may be useful for deciding upon the proper treatment methods.

We compared the therapeutic efficacy of the treatment for patients with TNM stage IVa HCC, in terms of TACI applied anticancer agents, and we analyzed the prognostic factors that influenced the survival rate.

MATERIALS AND METHODS

Between January 1996 and December 1998, 127 patients were diagnosed as having TNM stage IVa HCC, and they were treated at Yonsei University, College of Medicine, Seoul, Korea.

Subjects

To exclude other factors that could influence the survival rate, patients were included to the study only if they met the following conditions.

1) TNM stage IVa HCC at the time of diagnosis.
2) age less than 70.
3) good general activity (ECOG 0, 1, 2).
4) preserved hepatic function, including controllable ascites (Child-Pugh class A or B).
5) no coagulopathy.
6) no other medical illness that would affect the survival rate.

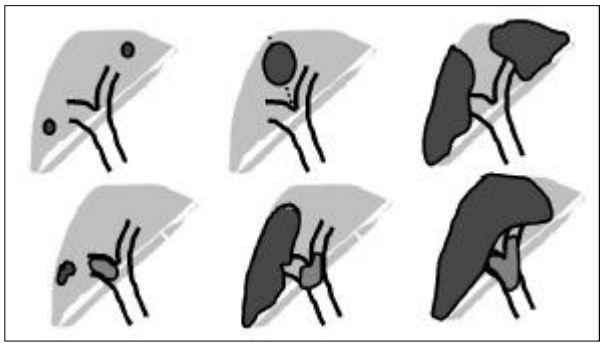

Fig. 1. TMN Stage IVa HCCs showing different shape and the vessel invasion status.

Treatment methods

The patients were divided into the intra-arterial adriamycin (Group I) and the intra-arterial cisplatin (Group II) infused groups according to the anticancer agents used. In Group I, a mixture of lipiodol (Andre Guerbet, Aulnay-sous-Bois, France) and doxorubicin hydrochloride (Adriamycin) (ADR; Il-dong, Seoul, Korea) (25 - 50 mg) was infused into the hepatic artery. In Group II, a mixture of cisplatin (DDP; Dong-A, Seoul, Korea) (80 - 100 mg/m^2) and lipiodol was infused. Depending upon the tumor size, 5 to 30 cc of a mixture of lipiodol- adriamycin or lipiodol-cisplatin was infused into the HCC feeding vessel by using a hydrostatic or an automatic syringe. If possible, a partial embolization procedure was undertaken with gelatin sponge particles (Gelform; Spongostan Standard, Ferrosan, Denmark) for the combined small multifocal lesions in both groups. TACI was performed every month in both groups. However, if a complete response was obtained, as measured according to tumor size, a longer interval of TACI was allowed for the treatment of HCC. Patients who were left untreated for whatever reasons were included into Group III.

Prognostic factors, response rate and survival

The prognostic factors that were selected as being likely to influence survival were age, gender, tumor size, type of tumor, PVT, bilobular involvement, Child-Pugh classification, total serum bilirubin levels, albumin level, alanine aminotransferase (ALT) level, alkaline phosphatase (ALP) level, alpha-fetoprotein (AFP) level and the response to treatment. Tumors were classified into three types (nodular, massive and diffuse type) according to Eggel system of classification[12] and this was done by assessment with abdominal ultrasonography, computer tomography and angiography.

Response rates, survival rates, side effects and toxicities with respect to treatment were compared. Because we believed that the assessment of treatment efficacy based on one therapeutic trial

was inadequate, 3 consecutive cycles of TACI were required for the analyses. Two cycles of therapy that led to a complete response at 3 months after the initial therapy were also included. Serum AFP values were monitored in those patients having a serum AFP value before chemotherapy that exceeded 20 ng/ml. Abdominal Computer Tomography (CT) and serum alpha-fetoprotein levels (AFP) at 3 months after the initial TACI treatment were analyzed to evaluate the response rate.

The tumor size was defined as the longest tumor diameter and by its summation in the case of multiple tumors. The tumor reduction rate was calculated using the following equations:

- Tumor size reduction rate=(long axis of tumor before chemotherapy-long axis of tumor after chemotherapy)(100/long axis of tumor before chemotherapy
- Serum AFP reduction rate=(serum AFP before chemotherapy-serum AFP after chemotherapy) (100/serum AFP before chemotherapy

Tumor responses to chemotherapy were defined as follows[13]: Complete response (CR) was the disappearance of tumor. Partial response (PR) was a reduction greater than 50%. Minor response (MR) was a reduction of 25% to 50%. No change (NC) was a change less than 25%. Progressive disease (PD) was an increase greater than 25% or the appearance of new lesion.

Statistics

Chi-square test, Student t-test and Cox's proportional hazard regression model were used for the analysis of clinical characteristics and prognostic factors. The Kaplan-Meier method was used to analyze the cumulative survival. The statistical difference, in all analyses, was accepted when the p value was lower than 0.05, and all statistical analyses were performed using Window SPSS release 7.0.

RESULTS

Clinical characteristics

The median age of total 127 patients was 55 years (male : female, 107 : 20). The most common causes of HCC were hepatitis B virus (HBV) infection (68.4%), followed by alcohol (8.7%), hepatitis C virus (HCV) infection (7.9%), and others (6.3%). In terms of the whole population, tumors larger than 5 cm in diameter were found in 89 patients (70.1%), the nodular type tumors were the most common (44.0%), and these were followed by the massive (29.2%) and diffuse (26.8%) type tumors. According to the Child-Pugh classification, 114 patients were Child A (89.8%), and 13 were Child B (10.2%). PVT was present in 80 patients (63.0%), and bilobular involvement was observed in 89 patients (70.1%) (Table 1).

Age, gender ratio, Child-Pugh classification and the causes of HCC were not significantly different between Groups I and II. However, the size and type of HCC, and the presence of PVT were significantly different (Table 1).

Prognostic factors

Univariate analysis showed that the tumor size (diameter > 5 cm), type of tumor, presence of PVT, age, serum albumin levels, total serum bilirubin and serum ALP levels at the time of diagnosis, and the tumor response (tumor size and serum AFP reduction rate) 3 months after chemotherapy significantly affected the survival rate. However, bilobular involvement of tumor, which is one of characteristics of TNM stage IVa, was not found to exert an influence on the survival rate, and the better the tumor response was at 3 months, then the longer was the survival time.

Multivariate analysis showed that the tumor size (p=.005), type of tumor (p=.000), serum albumin levels and total serum bilirubin levels at the time of diagnosis (p=.000, p=.006, respectively), and tumor size and serum AFP reduction rates 3 months after chemotherapy (p=.007, p=.002, respectively) significantly affected the survival rate (Table 2).

Therapeutic response

The median survival time of the patients excluded from analysis because they did not receive enough treatment cycles were 4.1 and 3.8 months in Group I (20 patients) and Group II (30 patients),

Table 1. Demographic Findings of Subjects

	Group I	Group II	Total	*p*-value
	N=71 (%)	N=56 (%)	N=127 (%)	
Sex (M:F)	59 : 12	48 : 8	107 : 20	NS
Age (Mean(SD)				NS
M:F	55 ± 8 : 59 ± 10	53 ± 9 : 55 ± 7	55 ± 9 : 55 ± 9	
Etiology				NS
HBV infection	52 (73.2)	35 (62.5)	87 (68.4)	
HCV infection	8 (11.3)	2 (3.6)	10 (7.9)	
Alcohol	4 (5.6)	7 (12.5)	11 (8.7)	
HBV+ Alcohol	4 (5.6)	7 (12.5)	11 (8.7)	
Others	3 (4.2)	5 (8.9)	8 (6.3)	
Child-Pugh class				NS
A	63 (88.7)	51 (91.1)	114 (89.8)	
B	8 (11.3)	5 (8.9)	13 (10.2)	
Tumor size (diameter)				0.015*
> 5 cm	43 (60.6)	46 (82.1)	89 (70.1)	
≤ 5 cm	28 (39.4)	10 (17.9)	38 (29.9)	
Type of tumor				0.002*
Nodular	41 (57.7)	15 (26.8)	56 (44.0)	
Massive	17 (23.9)	20 (35.7)	37 (29.2)	
Diffuse	13 (18.3)	21 (37.5)	34 (26.8)	
PVT	35 (49.3)	45 (80.4)	80 (63.0)	0.000*
Bilobular involvement	52 (73.2)	37 (66.1)	89 (70.1)	NS

*p <0.05. Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.

respectively, but the differences were not significant. The differences between the prognostic factors such as, tumor size, type of tumor, and the presence of PVT were also found not to be significant factors for the median survival time.

Survival period

During the follow-up periods (mean duration, 13.9 months), the overall median survival for stage IVa HCC patients was 6.3 months. Group I (10.0 months, Adriamycin) showed significant improvement in survival compared to Group II (5.7 months, Cisplatin) (p=.000).

After repeated chemotherapy, Group I showed better survival than Group II (14.0 vs 7.9 months) (Fig. 2, Table 3); the patients who received repeated chemotherapy showed greater survival than the above patients (10.0 vs 5.7 months) because we excluded the survival of patients who did not receive enough treatment cycles. However, when considering the other prognostic factors of HCC, Group I showed greater survival than Group II only for the cases of small tumor (diameter ≤ 5 cm) or for the nodular type of HCC

Table 2. Prognostic Factors Influencing Survival

	Univariate	Multivariate	
	p-value	Exp (B) (95% CI)	*p*-value
Tumor size (diameter)	0.000*	2.2 (1.28-3.90)	0.005*
Type of tumor	0.000*	1.9 (1.35-2.60)	0.000*
Albumin	0.005*	0.5 (0.33-0.70)	0.000*
Total bilirubin	0.018*	1.6 (1.15-2.29)	0.006*
Tumor response at 3 months after chemotherapy			
Tumor size	0.000*	1.5 (1.11-1.93)	0.007*
Serum AFP	0.000*	1.4 (1.11-1.64)	0.002*
PVT	0.000*	1.2 (0.77-1.94)	0.385
Age	0.006*	1.0 (0.95-1.00)	0.070
ALP	0.002*	1.0 (0.99-1.00)	0.900
Bilobular involvement	0.902		

*$p < 0.05$. CI, confidence interval.

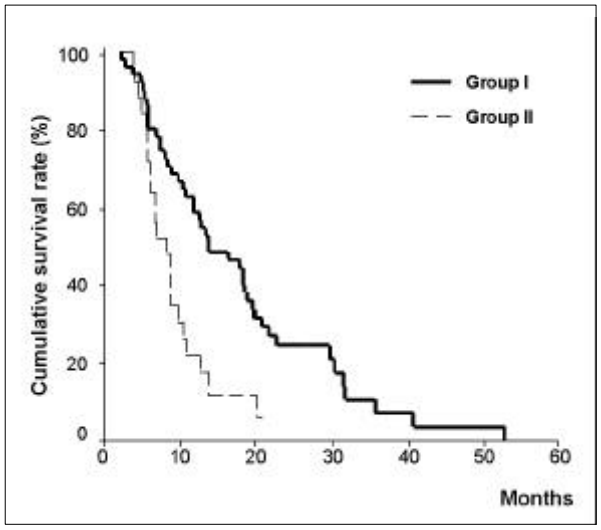

Fig. 2. Cumulative survival curves of Group I and Group II after repeated chemotherapy.

(Table 4). When the survival rates were compared between the two groups for those cases with nodular type of tumors, the clinical characteristics and therapeutic responses were not found to be different (Table 5). In this study, all the small HCCs were of the nodular type. For the large tumor (diameter > 5 cm), PVT or diffuse type, no significant difference could be attributed to the anticancer agents. When a bilobular tumor had PVT, the Group II seemed to live longer than Group I, but again this was not significant (Table 3).

Tumor response

The tumor size and serum AFP reduction rates (CR + PR) at 3 months were 25.5% and 59.1 % for Group I, and 7.8% and 42.1% for Group II, respectively (Table 6). At 6 months, the tumor size and serum AFP reduction rates (CR + PR) were 8.0% and 57.9% for Group I, and 0% and 25.0% in Group II, respectively. Tumor responses at 3 and 6 months were better for Group I than for Group II (Table 2).

Side effects of chemotherapy

Fever, anorexia, abdominal pain and an elevation of ALT level (to more than twice the normal level) were observed in Group I, and anorexia, nausea and fever were observed in Group II, in the descending order of frequency. Fever, abdominal pain, and elevated ALT level were noted significantly more often in Group I (Table 7).

Causes of death

Hepatic failure was the most common cause of

Table 3. Median Survival According to Prognostic Factors after Repeated Chemotherapy

	Group I		Group II		*p*-value
	N	Survival (months)	N	Survival (months)	
Total	51	14.0 ± 10.0	26	7.9 ± 4.5	0.001*
Type of tumor					
Nodular	36	18.4 ± 11.1	11	9.0 ± 5.8	0.029*
Massive	12	8.5 ± 7.2	9	7.2 ± 2.7	0.226
Diffuse	3	11.0 ± 5.3	6	6.7 ± 2.8	0.100
Tumor size (diameter)					
> 5 cm	27	10.8 ± 7.6	20	7.2 ± 4.3	0.103
≤ 5 cm	24	19.2 ± 11.3	6	8.0 ± 5.9	0.018*
PVT	21	8.5 ± 11.7	18	7.1 ± 4.1	0.051
PVT & Bilobular involvement	6	4.9 ± 4.2	11	7.0 ± 4.5	0.512

*$p<0.05$. Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.

Table 4. Significant Median Survival According to the Prognostic Factors after Repeated Chemotherapy without Embolizations

	Group I		Group II		*p*-value
	N	Survival (months)	N	Survival (months)	
Total	40	12.1 ± 7.0	24	7.5 ± 4.1	0.015*
Nodular type of tumor	25	15.2 ± 9.1	9	9.5 ± 5.8	0.041*
Small sized tumor (diameter ≤ 5 cm)	13	18.5 ± 6.6	4	8.8 ± 6.3	0.025*

*$p<0.05$. Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.

death (Table 8). Differences in causes of death were not statistically significant between the two groups. Two patients in Group II died due to the treatment related complications (cisplatin-induced uremia).

Comparison between treated group and untreated group

Although all the patients were classified as HCC stage IVa, the pretreatment prognostic factors of the treated group (Group I + II) and untreated group (Group III) differed. The median survival period of the treated group was significantly higher than that of the untreated group (6.3 vs 2.0 months, respectively, p=.000, Table 9). We believe that the prognostic factors and appropriate chemotherapies were primarily responsible for the difference of survival times.

DISCUSSION

For the treatment of unresectable advanced HCC, some of the available therapeutic options are intra-arterial chemoinfusion and embolization,[14-18] systemic chemotherapy,[19] immunotherapy,[20] ultrasonography guided ethanol injection,[21] radiotherapy,[22] thermotherapy and liver transplantation.[23] Although there have some positive responses attributed to these modalities, the results haven't always been very satisfactory. Among these methods, IAC has been the most widely performed procedure as a palliative treat-

Table 5. Characteristics and Therapeutic Responses of Nodular Typed HCC after Repeated Chemotherapy

	Group I	Group II	*p*-value
	N=36 (%)	N=11 (%)	
Sex (M : F)	31 : 5	11 : 0	0.322
Age (Mean ± SD)	56 ± 8	54 ± 10	0.469
Child-Pugh class			0.578
A	33 (91.7)	9 (81.8)	
B	3 (8.3)	2 (18.2)	
Tumor size (diameter)			
Maximal	4.7 ± 2.2	5.2 ± 1.9	0.455
> 5 cm	12 (33.3)	6 (54.5)	0.166
Albumin	3.9 ± 5.6	3.7 ± 0.5	0.359
Total bilirubin	1.1 ± 2.2	1.1 ± 0.6	0.657
ALT	44 ± 40	39 ± 23	0.729
ALP	110 ± 43	134 ± 78	0.197
PVT	10 (27.8)	6 (54.5)	0.101
Bilobular involvement	28 (77.8)	9 (81.8)	1.000
Tumor response at 3 months after chemotherapy			
Tumor size [CR : PR]	4 : 6 (11.1 : 16.7)	0 : 1 (0 : 9)	0.094
Serum AFP [CR : PR]	5 : 15 (16.1 : 48.4)	1 : 1 (14.3 : 14.3)	0.323

Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.
SD, standard deviation.

Table 6. The Responses after 3 Months of Chemotherapy According to Tumor Size and Serum AFP after Repeated Chemotherapy

	Tumor size		Serum AFP	
	Group I	Group II	Group I	Group II
CR	4 (7.8)	1 (3.9)	5 (11.4)	2 (10.5)
PR	9 (17.7)	1 (3.9)	21 (47.7)	6 (31.6)
MR	3 (5.9)	0 (0)	0 (0)	0 (0)
NC	8 (15.7)	6 (23.0)	6 (13.6)	3 (15.8)
PD	27 (52.9)	18 (69.2)	12 (27.3)	8 (42.1)
Total (%)	51 (100)	26 (100)	44 (100)	19 (100)

Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.

ment for patients with advanced HCC.

Adriamycin is one of the most frequently used anticancer agents for TACI; however, its efficacy has recently been challenged by cisplatin.[24-27] In several previous reports, the infusion of adriamycin into the hepatic artery for advanced HCC

Table 7. Side Effects of Group I and Group II

	Group I	Group II	Total
	N=71(%)	N=56(%)	N=127(%)
Anorexia	43 (60.6)	46 (83.6)	89 (70.1)
Nausea	33 (46.5)	38 (67.9)	71 (55.9)
Fever*	44 (62.0)	19 (33.9)	63 (49.6)
Elevation of ALT* (more than 2 times)	40 (56.3)	18 (32.1)	58 (45.7)
Abdominal pain*	40 (56.3)	15 (26.8)	55 (43.3)
Vomiting	20 (28.2)	25 (44.6)	45 (35.4)
Diarrhea	5 (7.0)	4 (7.1)	9 (7.1)
Headache	5 (7.0)	2 (3.6)	7 (5.5)
Cholecystitis	1 (1.4)	1 (1.8)	2 (1.6)
Hiccup	1 (1.4)	1 (1.8)	2 (1.6)

*$p<0.05$. between Group I and Group II; Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.

Table 8. Causes of Death

	Group I	Group II	Total
	N=49 (%)	N=44 (%)	N=93 (%)
Hepatic failure	36 (73.5)	34 (77.3)	70 (75.3)
Renal failure	7 (14.3)	4 (9.1)	11 (11.8)
Gastrointestinal bleeding	4 (5.6)	2 (4.5)	6 (6.5)
HCC rupture	2 (4.1)	4 (9.1)	6 (6.5)

Group I, intra-arterial adriamycin infusion; Group II, intra-arterial cisplatin infusion.

has resulted in a 10-40% response rate (CR+PR) and for a 3-7 month period of median survival.[28-33] Although the response rate was better than that of systemic chemotherapy, the survival period was not similarly improved. On the other hand, with intra-arterial cisplatin infusion, a response rate (CR+PR) of 20-50% has been quoted along with a median survival period of 5-15 months; so it seems that Cisplatin is more effective than other anticancer agents.[24-26] However, there are some problems in evaluating the results of TACI for patients with HCC. First, as stated by Okuda,[34] there are ethical and methodological problems. Second, it's not so easy to select patients with equivalent conditions when considering such variables as tumor factors, hepatic function and anticancer drugs.[35-37] In other words, there are so many interactive factors such as sex, age, Okuda stage, Child-Pugh classification, serum AFP level, serum total bilirubin level, tumor size, type of tumor, the presence of PVT, extrahepatic metastasis, therapeutic modalities and tumor response to treatment; all of these are known to affect the prognosis, and it is hard to compare the efficacy of treatment modalities and prognosis under equivalent conditions. Therefore, the real indication of TACI for unresectable HCC has yet to be established.

To date, a number of studies have been undertaken to examine the influence of a relatively small number of prognostic factors upon advanced HCC. However, there has been no selec-

Table 9. Median Survival and Prognostic Factors of Group I+II and Group III

	Group I+II	Group III	*p*-value
	N=127 (%)	N=26 (%)	
Survival (mon)	6.3 ± 9.1	2.0 ± 5.6	0.000*
Sex (M : F)	107 : 20	24 : 2	NS
Age (Mean ± SD)	54 ± 8	49 ± 10	0.005*
Child-Pugh class			0.000*
A	114 (89.8)	11 (42.3)	
B	13 (10.2)	15 (57.7)	
Tumor size (diameter)			
Maximal	7.2 ± 3.6	9.1 ± 3.9	0.048*
> 5 cm	87 (68.5)	21 (80.8)	NS
Type of tumor			0.049*
Nodular	56 (44.1)	5 (19.2)	
Massive	37 (29.1)	11 (42.3)	
Diffuse	34 (26.8)	10 (38.5)	
Albumin	3.8 ± 0.5	3.4 ± 0.6	0.006*
Total bilirubin	1.2 ± 0.5	2.7 ± 2.8	0.000*
ALT	51 ± 54	94 ± 110	0.003*
ALP	156 ± 96	295 ± 178	0.000*
PVT	80 (63.0)	24 (92.3)	0.003*
Bilobular involvement	89 (70.1)	14 (53.9)	NS

*p<0.05. between Group I + II and Group III; Group I+II, intra-arterial adriamycin or cisplatin infusion; Group III, No treatment; NS, not signibicant.

tive study of TNM stage IVa HCC. By selecting only those patients with TNM stage IVa HCC, we attempted to more accurately compare the efficacy of TACI using two different anticancer agents, and we simultaneously tried to identify the prognostic factors, other than TNM stage, that could affect the response to treatment and the survival rate. In our present study, the response rates, as were evaluated by tumor size and serum AFP reduction rates 3 and 6 months after chemotherapy, were found to be higher in Group I than in Group II; moreover, the survival period was also extended in Group I. However, these results might not be solely due to the effect of the anticancer agents because not all the prognostic factors were initially same for the two groups of patients. After eliminating the confounding factors, we re-compared the therapeutic efficacy and we found that for small or nodular HCC, Group I proved to have a clear survival benefit, yet for larger tumors, PVT or those patients with bilobular involvement, the median survival period was not significantly different between the two groups. However, regardless of treatment methods, the independent clinical impact of prognostic factors such as tumor size, type of tumor and PVT, which were initially different between the two groups in this study, still remains.

Tumor size, type of tumor, serum albumin level and total bilirubin level at the time of diagnosis,

and tumor responses 3 months after chemotherapy were the significant prognostic factors. Among these, tumor responses 3 months after chemotherapy might be useful to decide whether to continue anticancer treatment. Main PVT represents the status of progressive vascular invasion, and it usually means that the hepatic function is inadequate for the patient to undergo hepatic artery embolization. Although there have been a small number of reports that have shown favorable results for HCC with main PVT,[38] our study did not demonstrate good survival rates when the presence of PVT was observed. Interestingly, HCCs larger than 5 cm in diameter had a poor prognosis, and yet bilobular tumor was not a significant factor for a poor prognosis. The association between tumor size and disease progress has been reported in other studies.[39,40] It also has been reported that when the tumors selected for study had the same TNM stage IVa of HCC, that due to the recent development of the treatment method, multiple HCC involving both lobes had a better survival rate than other advanced HCCs, including HCCs with PVT. These researchers also found that its survival rate was not different from that of TNM stage III HCC, which supports the newly modified TNM staging system.[41-43] For stage IVa advanced HCC, the tumor size and type should be considered together with PVT and bilobular involvement in determining the choice of therapeutic modalities.

This retrospective study has some limitations including the use of additional embolizations for multifocal small lesions, which were carried out in 11 patients of Group I and in only 2 patients of Group II due to Group II's higher rate of portal vein thrombosis. Since embolizations were performed only for small satellite lesions in small number of patients, the effect on the survival rates might not be so significant. However, additional gelform embolizations per se might have improved the patients' survival. When we excluded data from the patients who had undergone gelform embolizations, the level of statistical power for the improvement of survival was reduced, but this adjustment did not change the statistical significance (Table 4). For the small tumors small or for tumors in both lobes, we believed that a combined treatment involving intra-arterial adriamycin infusion with embolization, when possible, could improve the survival rate, and this study demonstrated this possibility. In addition, we have shown that even in TNM stage IVa HCC, there could be important prognostic factors other than the TNM stage, and that treatment based upon these prognostic factors might prolong the patients' survival time (Table 9).

In conclusion, Group I showed a better survival time than Group II for advanced HCCs of TNM stage IVa, yet when considering the other prognostic factors, no significant difference between the survival rates for the two groups was found, with the exception of small size tumor or nodular HCCs.

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