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ORIGINAL ARTICLE

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Therapeutic efficacy of multimodal combination therapy using transcatheter arterial infusion of epirubicin and cisplatin, systemic infusion of 5-fluorouracil, and additional percutaneous ethanol injection for unresectable hepatocellular carcinoma

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Abstract *Purpose*: Previous studies have shown that a treatment regimen using epirubicin, cisplatin, and 5-fluorouracil (5-FU) (ECF) has a survival benefit for gastric cancer patients. Based on these results and the hypothesis that a combination modality has a better therapeutic advantage over a single mode of therapy, the efficacy of multimodal combination therapy using a transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU, and additional percutaneous ethanol injection (PEI) for unresectable hepatocellular carcinoma (HCC) was investigated in this study in comparison with conventional transarterial chemoembolization (TACE). *Patients and methods*: From July 1997 to September 1998, a total of 52 patients with unresectable HCC who underwent at least two cycles of transarterial chemotherapy were enrolled in this study. Among the 52 patients, 30 (ECF group) received a multimodal combination therapy comprising transarterial infusion of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2), systemic infusion of 5-FU (200 mg/m^2), and additional PEI every 4 weeks, and the remaining 22 (ADR group) received conventional TACE using Adriamycin (ADR, 50 mg) and Gelfoam every 8 weeks. *Results*: During the follow-up period (mean 13.8 ± 8.5 months), the objective tumor response of the ECF group was significantly higher than that of the ADR group (53.3 vs 22.7%, $P = 0.044$). The median survival time was 13.5 months for the ECF group and 10.5 months for the ADR group ($P = 0.026$). The cumulative survival rates at 6, 12, 18, and 24 months, respectively, were 90, 57, 27, and 17% for the ECF group and 73, 37, 7, and 0% for the ADR group. Univariate analysis showed five prognostic factors including tumor number, tumor morphology, portal vein thrombosis, Child-Pugh classification, and tumor response. With multivariate analysis, portal vein thrombosis and tumor response were identified as the two independent factors for survival. No serious adverse effect was observed in the ECF group, while there was a higher tendency for hepatic complications in the ADR group. *Conclusions*: Combination therapy comprising transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU, and additional PEI appears to be feasible and promising as a multimodal approach for unresectable HCC. Furthermore, it may provide a survival benefit for patients with more advanced disease.

Keywords Hepatocellular carcinoma · ECF regimen · Percutaneous ethanol injection · Combination therapy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases in the world with a high incidence in Asia and Africa. Surgical resection and liver transplantation can increase the chance of cure. However, there are few cases in which surgery has been curative due to the associated liver cirrhosis and multifocal lesions. Despite surveillance programs for high-risk

patients, it is still a medical issue that many patients have an unresectable HCC at the time of diagnosis [5, 11]. In this regard, transarterial chemoembolization (TACE) has been widely used as a palliative treatment for unresectable HCC [2, 4, 6–8]. Locoregional therapy including percutaneous ethanol injection (PEI), cryoablation, or radiofrequency ablation can be used for patients with a relatively small size and small number of tumors, but has some limitations [5]. In order to maximize the therapeutic efficacy of each treatment, the appropriate combination of modalities is essential. A combination regimen of epirubicin, cisplatin, and 5-fluorouracil (5-FU) (ECF) has been evaluated in gastrointestinal cancer. Several randomized clinical trials using an ECF regimen have shown a survival benefit in patients with advanced gastric carcinoma [13, 14]. Unfortunately, systemic chemotherapy using this regimen has been reported to be unsuccessful in HCC [1]. To the best of our knowledge, there is a lack of data on the combined transarterial and systemic approach using an ECF regimen in HCC. The concept of combination and multimodality led us to conduct this study.

In this study, as a multimodal treatment for unresectable HCC, we evaluated the therapeutic efficacy of combination therapy comprising transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU, and additional PEI in comparison with conventional TACE using Adriamycin (ADR) and Gelfoam. We report here the survival rate and the prognostic factors for survival as well as the adverse effects of each regimen.

Patients and methods

Patient selection

From July 1997 to September 1998, a total of 141 patients were newly diagnosed with unresectable HCC in our liver clinic. The diagnosis of HCC was based on histologic and cytologic evidence, or elevated serum alfa-fetoprotein (AFP) levels (>400 ng/ml) with typical radiologic findings. Of the 141 patients, 52 who completed at least two cycles of transarterial chemotherapy using either ECF or ADR were enrolled in this study. Patients with distant metastasis or main portal vein thrombosis at the time of enrollment were excluded. Of these 52 patients, 30(ECF group) received multimodal combination therapy comprising transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU, and additional PEI. The remaining 22 patients (ADR group) received conventional TACE comprising Adriamycin and Gelfoam. Follow-up of the study population was continued until October 2002.

Therapeutic procedures

Before the procedure, all patients were fasted overnight. In order to prevent renal toxicity, intravenous hydration of 2 l saline with diuretics was given to all patients in the ECF group. The femoral artery was catheterized under fluoroscopy, and a portogram and hepatic arteriogram were obtained to reveal portal vein thrombosis and to estimate the size, shape, and location of the tumors. Patients in the ECF group underwent transarterial infusion of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) in a mixture of 5–10 ml Lipiodol (Guerbet, Aulnay-sous-Bois, France), and after the transarterial session, they received a systemic infusion of 5-FU (200 mg/m^2) for 12 h. Patients in the ADR group underwent transarterial infusion of Adriamycin (50 mg) followed by embolization with Gelfoam (Spongostan, Johnson & Johnson Medical, Gargrave, UK). PEI was performed only in patients in the ECF group. Unless there was a contraindication, the sessions were repeated every 4 weeks in the ECF group and every 8 weeks in the ADR group. The dose was modified or the treatment interval was prolonged whenever a hepatic dysfunction or other serious adverse effects developed. PEI was performed under real-time ultrasound (Kretz Combison 530 unit, Kretz, Zipf, Austria). A 15-cm 22-gauge Chiba needle was introduced percutaneously into the target area through a puncture probe under ultrasound guidance, and 1–15 ml 98% ethanol was slowly injected. According to the follow-up radiologic findings, the PEI courses were repeated at least 2 days apart if necessary.

Adverse effects and drug modification

The adverse effects were assessed for 1–2 weeks after each cycle and at admission for the next cycle. The adverse effects of grade 3 or more were graded according to the NCI-CTC criteria, version 2.0. During the treatment periods, the dose of chemotherapeutic agents was adjusted to the performance status or the liver function of the patients in order to reduce the adverse effects or toxicity. Based on our experience, the following formula for dosage modification was derived: administration dosage $=$ D $\times$ BSA $\times$ M where D is initial dosage of each agent, BSA is body surface area, and M is the modification rate $=$ (white blood cell count/4000) $\times$ (1$-$(age$-$45)/100) $\times$ (1$-$(Child-Pugh score$-$5)/10). According to this formula, the administration dosage of each chemotherapeutic agent was modified. Only the Child-Pugh score was calculated using this formula if the patient's white blood cell count was >4000/mm^3 or the patient's age was <45 years.

Assessment of treatment response

After the second cycle, tumor response was assessed at intervals of 1–2 months (mainly prior to each cycle) using a contrast-enhanced CT scan. The two longest lines crossing on the CT scan were used to measure the tumor size. Serum AFP levels were also serially checked. A complete response (CR) was defined as the radiologic

disappearance of the tumors with a normalization of the serum AFP level. A partial response (PR) was defined as a 50% or more reduction in the product compared with the baseline measurement. Progressive disease (PD) was defined as a 25% or more increase in the product, or newly developed nodules, and stable disease (SD) was defined as a status that did not meet the above three response criteria. The AFP response was also assessed using above criteria. The objective response was defined as the sum of the CR and PR.

Statistical analysis

The results were analyzed using Student's *t*-test, the chi-squared test, and Fisher's exact test. Patient survival was calculated from the beginning of treatment to the date of death. The cumulative survival rates were estimated using the Kaplan-Meier method, and differences were analyzed with the log-rank test. The possible factors that proved to be of statistical significance in a univariate analysis were subsequently estimated using the multivariate Cox proportional hazard model. Using SPSS 10.0, a P values < 0.05 were considered significant.

Results

Patient characteristics

The baseline characteristics of all 52 patients are summarized in Table 1. Age, sex, hepatitis B surface antigen (HBsAg) status, Child-Pugh classification, tumor size, tumor number, tumor morphology, and the presence of portal vein thrombosis were not significantly different between the two groups. The serum AFP level was higher in the ECF group than in the ADR group (1060.3 ± 749.1 vs 574.4 ± 680.3 ng/ml; $P = 0.020$).

Table 1 Baseline characteristics of 52 HCC patients

	ECF group ($n = 30$)	ADR group ($n = 22$)	P value
Age (years)	54.3	57.0	0.171
Sex (male/female)	27:3	18:4	0.438
HBsAg seropositivity	25	15	0.318
Child-Pugh classification			0.639
A	28	19	
B	2	3	
AFP (ng/ml)	1060.3 ± 749.1	574.4 ± 680.3	0.020
< 20	2	5	
20–200	5	5	
> 200	23	12	
Tumor size (cm)	8.6 ± 2.8	9.9 ± 4.0	0.187
Tumor number	2.3 ± 1.7	1.8 ± 0.5	0.149
Tumor morphology			0.614
Nodular	11	8	
Diffuse	19	14	
Portal vein thrombosis			0.424
Present	13	12	
Absent	17	10	

Tumor response

No CR was observed in this study during the mean follow-up period of 13.8 months (range 3–50 months). In the ECF group, 16 patients (53.3%) showed a PR, 4 (13.3%) progressed, and 10 (33.3%) had a stable tumor size. In the ADR group, 5 patients (22.7%) showed a PR, 5 (22.7%) progressed, and 12 (54.5%) had a stable tumor size. Therefore, the objective tumor response in the ECF group was significantly higher than that in the ADR group (53.3 vs 22.7%, $P = 0.044$; Fig. 1). With regard to AFP levels, 45 patients were available for assessment of the AFP response because 7 patients showed a normal baseline AFP level (≤ 20 ng/ml). In the ECF group, the AFP level was normalized in 5 patients (17.9%) and reduced by more than half in 10 patients (35.7%), whereas in the ADR group, the AFP level was normalized in only 1 patient (5.9%) and reduced by more than half in 3 patients (17.6%). The stabilization and progression rate in the AFP level was 28.6% and 17.9% in the ECF group, and 52.9% and 23.5% in the ADR group, respectively. Although a significant statistical impact was not observed, there was a tendency toward a higher objective response rate of the AFP level in the ECF group than in the ADR group (53.6% vs 23.5%, $P = 0.065$). The number of chemotherapy cycles was larger in the ECF group (7.0 ± 2.9 vs 3.8 ± 1.3, $P = 0.004$), whereas the mean interval between each cycle was longer in the ADR group (4.4 ± 1.2 vs 8.3 ± 3.7 weeks, $P = 0.011$). A total of 126 courses of additional PEI with a mean of 4.2 courses per patient (range 1–21) were performed in the ECF group only. PEI was carried out in 73% (22/30) of the ECF group. There was no significant difference in treatment response between patients with and without PEI in the ECF group ($P = 0.412$). Table 2 summarizes the clinical results in the two groups.

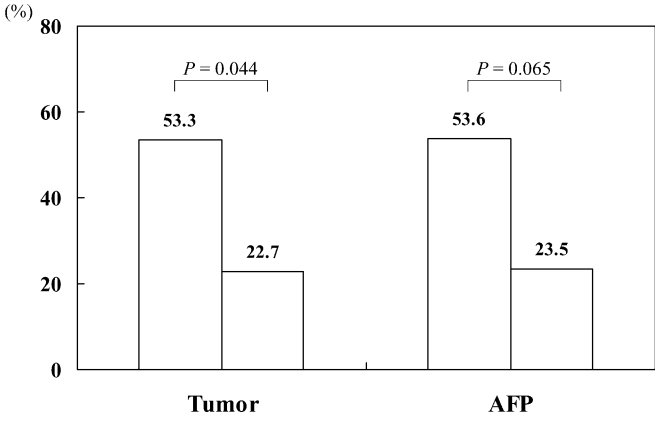

Fig. 1 Comparison of objective tumor and AFP response rates between the ECF group (*left bar of each pair*) and the ADR group (*right bar of each pair*). Objective response: CR + PR

Table 2 Clinical results in the two groups

	ECF group ($n=30$)	ADR group ($n=22$)	P value
Tumor response			
CR (%)	0	0	
PR (%)	16 (53.3%)	5 (22.7%)	
SD (%)	10 (33.3%)	12 (54.5%)	
PD (%)	4 (13.3%)	5 (22.7%)	
Objective tumor response[a]	16 (53.3%)	5(22.7%)	0.044
AFP response ($n=45$)			
CR (%)	5 (17.9%)	1 (5.9%)	
PR (%)	10 (35.7%)	3 (17.6%)	
SD (%)	8 (28.6%)	9 (52.9%)	
PD (%)	5 (17.9%)	4 (23.5%)	
Objective AFP response[a]	15 (53.6%)	4 (23.5%)	0.065
Number of chemotherapy cycles	7.0 ± 2.9	3.8 ± 1.3	0.004
Interval between cycles (weeks)	4.4 ± 1.2	8.3 ± 3.7	0.011
PEI course	4.2 ± 4.1	0	<0.001
Median survival time (months)	13.5	10.5	0.026

[a]Objective response was defined as the sum of CR and PR.

Survival rate and prognostic factors

During the follow-up period, 29 of 30 patients in the ECF group and 21 of 22 patients in the ADR group died. One patient in the ECF group was still alive at the end of the study period, and one patient in the ADR group was lost after a follow-up of 17 months. The survival curve is shown in Fig. 2. Actuarial survival was significantly better in the ECF group than in the ADR group ($P=0.026$; Table 2). The cumulative survival rates at 6, 12, 18, and 24 months, respectively, were 90%, 57%, 27%, and 17% in the ECF group and 73%, 37%, 7%, and 0% in the ADR group. The median survival times of the ECF group and ADR group were 13.5 and 10.5 months, respectively. Among the ECF group, survival time was not different in patients with and without PEI ($P=0.537$). Univariate analysis revealed five possible factors affecting the survival: tumor number, tumor morphology, portal vein thrombosis, Child-Pugh classification, and tumor response (Table 3). Multivariate analysis of these five factors showed that portal vein thrombosis and tumor response were the two independent factors for survival (Table 4). Using continuous variables, tumor size was also significant for survival ($P=0.045$), but the statistical power disappeared ($P=0.247$) when it was stratified into two groups (>5 or ≤ 5 cm).

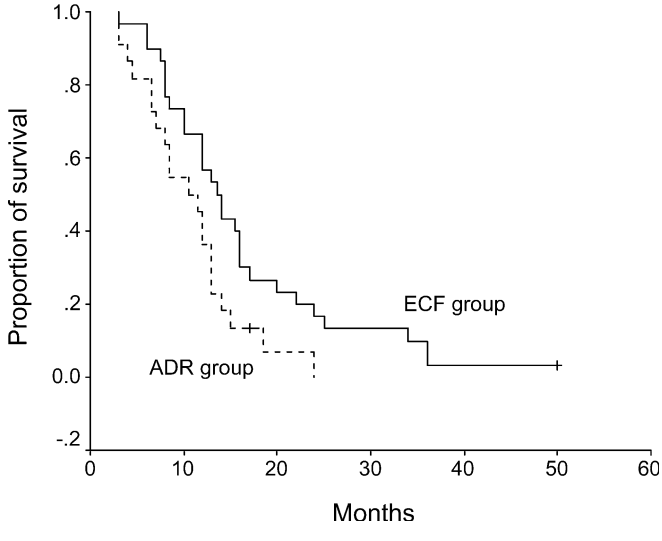

Fig. 2 Survival curves of the ECF group and the ADR group (log-rank test, $P=0.026$)

Adverse effects

The most frequent side effects in the two groups were fever, abdominal discomfort, headache, and nausea. None of the patients in the ECF group showed serious side effects. However, nine patients (40.9%) in the ADR group showed elevated aminotransferase or bilirubin levels after TACE, and three (13.6%) of them eventually stopped further cycles of TACE due to the hepatic complications after completing two cycles. Neutropenia was noted in four patients (13.3%) in the ECF group, which improved spontaneously in all patients a few days later. Overall, hematologic complications appeared to be more frequent in the ECF group, whereas hepatic complications appeared to be more frequent in the ADR group. Table 5 summarizes the adverse effects in the two groups. For the PEI procedures, there were no serious complications except for transient local pain or minimal needle track bleeding.

Table 3 Univariate analysis of prognostic factors for survival

Factor	P value
Age (>60 vs ≤ 60 years)	0.382
Sex (male vs female)	0.343
Tumor size (>5 vs ≤ 5 cm)	0.247
Tumor number (uninodular vs multiple)	0.015
Tumor shape (nodular vs diffuse)	0.001
Portal vein thrombosis (present vs absent)	<0.001
Child-Pugh classification (A vs B)	0.040
AFP level (>400 vs ≤ 400 ng/ml)	0.702
Tumor response (CR + PR vs SD + PD)	<0.001

Table 4 Multivariate analysis of five prognostic factors in the Cox regression model

Factor	P value
Tumor number (uninodular vs multiple)	0.066
Tumor shape (nodular vs diffuse)	0.235
Portal vein thrombosis (present vs absent)	0.031
Child-Pugh classification (A vs B)	0.572
Tumor response (CR + PR vs SD + PD)	0.015

Table 5 Adverse effects of 52 patients according to treatment group

	Number of patients (%)	
	ECF group ($n=30$)	ADR group ($n=22$)
Fever (≥38.0°C)	2 (6.7%)	2 (9.1%)
Nausea/vomiting	2 (6.7%)	1 (4.5%)
Hepatitis	5 (16.7%)	9 (40.9%)
Ascites	1 (3.3%)	3 (13.6%)
Neutropenia	4 (13.3%)	1 (4.5%)
Thrombocytopenia	1 (3.3%)	1 (4.5%)
Renal insufficiency	0 (0%)	0 (0%)
Gastrointestinal bleeding	0 (0%)	2 (9.1%)

Discussion

Despite the recent advances in new treatment modalities for HCC, the prognosis of patients with unresectable HCC is still disappointing. For the last two decades, TACE has been taking the lead as a palliative therapy for unresectable HCC [2, 6, 7], and more recently, PEI and radiofrequency ablation have been employed for relatively small tumors [5, 11]. Of the agents for transarterial chemotherapy, Adriamycin and cisplatin have been frequently used as a regimen, and have been reported to show considerable efficacy [2, 6, 7, 10]. A synergistic effect of 5-FU with cisplatin has been shown in experimental models [3], and a combination using an ECF regimen has shown a better survival benefit in gastric cancer patients [13, 14]. In general, the tumor cells in HCC receive their blood supply mainly from the hepatic artery, which underlies the basic concept of transarterial chemotherapy. Taking these findings into consideration, a combination using a transarterial infusion of epirubicin and cisplatin, and a systemic infusion of 5-FU may be one of the better options for treating unresectable HCC. Moreover, in this study PEI procedures were used as an adjuvant in the patients in the ECF group. PEI courses in this study were mainly attempted for a continuously viable tumor area on CT scan and angiography after at least two cycles. Although PEI is commonly indicated in patients with HCC of <3 cm and less than three lesions [11], repeated and well-targeted PEI courses can be properly used for the viable tumor cells resistant to TACE in patients with relatively large tumors as well. Taken together, the appropriately combined modality described in this study may have provided a survival benefit in the ECF group.

With regard to adverse effects, the ECF regimen was well tolerated and did not show major toxicity. Most frequent symptoms of all patients were a mild fever, headache, and nausea, which spontaneously regressed a few days later. Neutropenia was noticed more frequently in the ECF group. This might have been caused by the systemic effect of 5-FU in addition to the hypersplenism resulting from the underlying liver cirrhosis. On the other hand, hepatic complications were more common in the ADR group. This suggests that Gelfoam embolization in the ADR group possibly resulted in greater ischemic injury in the liver than Lipiodol in the ECF group. It has been found that chemoembolization using Lipiodol but without Gelfoam has a relatively lower therapeutic efficacy [9]. However, Gelfoam as an embolizing agent may not always be beneficial in HCC patients undergoing TACE. In a proportion of patients with an advanced stage or poor hepatic function, it can be harmful rather than effective, causing serious hepatic ischemic injury or vascular damage. Notably, our study showed that approximately 14% of the patients in the ADR group could not undergo further TACE courses due to the hepatic complications.

In the present study, the ECF group showed higher rates of both objective tumor response and survival than the ADR group. Univariate analysis revealed five factors indicating a poor prognosis including multiple nodules, diffuse morphology, Child-Pugh classification B, the presence of portal vein thrombosis, and a poor tumor response. Multivariate analysis of these five factors by the Cox regression model identified portal vein thrombosis and tumor response as the two independent factors for survival. Portal vein thrombosis as a factor indicating a poor prognosis is in accordance with a previous result [7], while the association between tumor response and survival is still a matter of controversy [2, 4, 7, 8].

It should be noted that the patients with unresectable HCC in this study were in a more advanced stage. The tumor extent was grave, and a high proportion of the patients had portal vein thrombosis. Moreover, the hepatitis B virus is endemic in Korea, and most of the patients had hepatitis B surface antigenemia, which has been characterized as indicating a poor prognosis among HCC patients [12]. Such poor prognostic features in our patients were reflected in the relatively short survival compared to that in other studies [6, 7]. Nevertheless, patients in the ECF group showed a better survival than patients in the ADR group. As mentioned above, a survival benefit in the ECF group may have been achieved as a result of the successful combination of transarterial systemic chemotherapy, and additional PEI, as well as a more protective dose of Lipiodol, not using Gelfoam. However, it is unclear if this regimen would provide a survival benefit in HCC patients with a smaller tumor size, well-preserved function, lack of portal vein thrombosis, and/or non-viral etiology.

This study was not a well-controlled prospective study. Nevertheless, the patients in the two groups had fairly similar characteristics with regard to age, sex, viral etiology, Child-Pugh classification, tumor size, tumor number, tumor morphology, and portal vein thrombosis. Our study had two other limitations. The first is that our patients had a relatively advanced HCC at presentation, and most of them had the hepatitis B virus. Therefore, it may be difficult to extend our results to patients with less-advanced HCC without viral infection. Second, a conservative group was not included in this study, and thus it is unclear if the treatment itself can

provide a survival benefit and promote the quality of life compared with conservative management.

To date, there has been no standard protocol for unresectable HCC, but new techniques and strategies are being developed. The results of each treatment are conflicting. This might be due to the differences in the study populations, the etiology, and treatment regimens. To enhance the therapeutic efficacy, appropriate combination of currently available treatment modalities may be necessary. HCC patients have heterogeneous tumor characteristics and hepatic reserve function. Therefore, the treatment design for HCC should be well tailored and individualized. The regimen described in this study included transarterial, systemic, and locoregional modalities in combination. Moreover, in order to preserve the patients' hepatic function as much as possible, this study individualized the dosage of agents using our modification method, and a less-toxic dose of Lipiodol was used. The number of PEI courses was also individualized according to the treatment response.

In fact, the main protocol for patients in the ECF group was combined transarterial and systemic chemotherapy using the ECF regimen. PEI was performed in patients who had no objective tumor response after at least two cycles. It was used as an adjuvant and an additional tool for the residual tumor area of HCC because the efficacy of PEI alone would be insufficient for the treatment of advanced unresectable HCC. It is unclear which modality provided the most successful results in this clinical setting. Based on the study results and our own experience, each modality in the current study was designed and combined to work synergistically. Therefore, we believe that the therapeutic gain was a consequence of the combination of each modality rather than a single mode of therapy. Basically, the aim of our study was not to compare the benefit of each modality, but to evaluate the therapeutic efficacy of multimodal combination therapy as a whole. Given that there is no standardization in the treatment of unresectable HCC because of the complex nature of the tumor, underlying liver, and patient characteristics, each modality should be appropriately combined and well-designed individually to enhance the efficacy of each. In this regard, our multimodal approach may offer another option for a tailored therapy.

In conclusion, this combination therapy comprising transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU, and additional PEI appears to be a feasible and promising multimodal approach for treating unresectable HCC. Furthermore, this approach would be expected to provide a survival benefit in patients with relatively advanced HCC. Our data again suggest that the optimal combination modality is more advantageous than single therapy. More studies will be needed to determine the best strategy for patients with unresectable HCC.

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