

Effects of transcatheter arterial chemoembolization with oral chemotherapy on hepatic neoplasmas

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Summary. An investigation was carried out into the effects of lipiodol-transcatheter arterial chemoembolization (L-TACE) therapy on hepatocellular carcinoma (HCC) and metastatic liver cancer, as well as the effects of oral 5-fluorouracil administration after L-TACE. For L-TACE, lipiodol mixed with adriamycin (doxorubicin) was injected through a catheter inserted into the tumor feeding artery and this was followed by embolization with a gelatin sponge. Twenty national hospitals throughout Japan participated in this multicenter co-operative open trial. A total of 102 patients became the subjects of study, including 75 HCC patients, 12 metastatic liver cancer patients treated with L-TACE, and 15 HCC patients who had hepatectomy after L-TACE. In 22% of the HCC patients and in 42% of the metastatic liver cancer patients, the tumor size was reduced by more than 50% after L-TACE. 73% of the 63 HCC patients showed a more than 50% reduction of the levels of serum α -fetoprotein. Although the survival rates of the HCC patients who had a hepatic resection were better than those who had not, there was no statistically significant difference between the survival rates of the HCC patients and those of the metastatic liver cancer patients treated with L-TACE. The survival rates of the HCC patients after L-TACE did not change as a result of oral 5-fluorouracil administration. It was therefore concluded that L-TACE is an effective way of treating both HCC patients and metastatic liver cancer patients, and that repeated L-TACE should be considered for some patients whose serum levels of α -fetoprotein rose again after L-TACE. Further follow-up studies will be needed to discover the effects of oral chemotherapy after L-TACE.

Introduction

Transcatheter arterial embolization (TAE) has been considered an effective method of treatment for hepatic neoplasms [6], but its value is limited because it is not effective enough on small daughter nodules, tumor thrombi and capsular invasions [5]. An oily lymphographic agent, lipiodol, has been known to be retained in selective tumor vessels for a long period of time, even in small daughter nodules [7]. Anticancer agents can also be expected to remain in the tumor for long periods if they are injected as a

mixture with lipiodol [2, 4]. Currently, combination therapy using lipiodol, adriamycin, and conventional TAE, termed lipiodol-transcatheter arterial chemoembolization (L-TACE), is the most powerful treatment for unresectable hepatic neoplasms. We therefore investigated the effects of L-TACE on liver cancers and the effects of 5-fluorouracil tablets administered orally after L-TACE. The study was carried out by 20 national hospitals throughout Japan as a multicenter co-operative open trial.

Table 1 lists the members of the Japanese National Hospitals Multicenter Study Group for Liver Cancer Treatment, Chaired by Toshitsugu Oda, MD, the director of the National Medical Center Hospital, Japan, who organized this clinical trial.

Table 1. The Japanese National Hospitals Multicenter Study Group for Liver Cancer Treatment

Chairman: Toshitsugu Oda (National Medical Center Hospital)

T. Sakurai	(National Sapporo Hospital)
Y. Tominaga	(National Dohoku Hospital)
Y. Kunii	(National Sendai Hospital)
T. Sato	(National Koriyama Hospital)
J. Inoue	(National Oji Hospital)
T. Saoshiro	(National Oji Hospital)
S. Kawai	(National Medical Center Hospital)
S. Mikuriya	(National Medical Center Hospital)
Y. Shimamura	(National Matsudo Hospital)
A. Takahashi	(National Matsudo Hospital)
A. Obayashi	(National Tokyo Hospital)
H. Saito	(National Tokyo Hospital)
A. Abe	(National Sagami Hospital)
T. Fujita	(National Yokosuka Hospital)
M. Horisawa	(National Nagoya Hospital)
K. Hara	(National Osaka Hospital)
M. Masuzawa	(National Osaka Hospital)
Y. Hada	(National Kure Hospital)
E. Kaneto	(National Osaka Hospital)
K. Kawaguchi	(National Iwakuni Hospital)
T. Harada	(National Shimonoseki Hospital)
Y. Yumoto	(National Shikoku Cancer Center Hospital)
K. Jinno	(National Shikoku Cancer Center Hospital)
O. Hara	(National Oita Hospital)
M. Yano	(National Nagasaki Chuo Hospital)
M. Furukawa	(National Nagasaki Chuo Hospital)
I. Arita	(National Kumamoto Hospital)
K. Fujimura	(National Kumamoto Hospital)
M. Makino	(National Minami Kyushu Chuo Hospital)

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Materials and methods

At 20 national hospitals, 117 patients with hepatocellular carcinoma (HCC) or metastatic liver cancer were treated between March 1986 and February 1987. The patients who became the subjects of study had to satisfy the following criteria [1]: the diagnosis was HCC or metastatic liver cancer [2]; the diagnosis was made histologically in patients who had had laparotomy [3]; in patients who had had no laparotomy, the diagnosis was made by α -fetoprotein (AFP) tests and imaging procedures such as computerized tomography, ultrasonography and angiography [4]. The laboratory data fulfilled the following limitations; iodycyanine green (R15) <30%; GOT and GPT <300 IU/l; white blood cell count >3000/mm³; and platelets >50000/mm³ [5]. Patients who had received previous treatment were also allowed to participate but patients who had a cardiac disease or severe complications were excluded.

As for the treatment, a vascular catheter was selectively inserted into the tumor feeding artery. 5–10 ml lipiodol (Lipiodol Ultra Fluid, an ethyl ester of poppyseed oil fatty acids containing 38% iodine) were mixed with adriamycin (doxorubicin) (20–50 mg/m²) dissolved in a contrast medium, Urografin. The mixture was injected through the catheter and this was followed by the infusion of cubes of gelatin sponge. In the 15 patients with HCC, a hepatic resection was performed about 2 weeks after L-TACE. Patients were prescribed 5-fluorouracil tablets (150–200 mg/body/day) after L-TACE until the total dose reached 10 g.

The serum levels of AFP, the size of the tumor, and the side-effects were checked and recorded on case cards. The

cards were submitted and processed at the end of the study period. The survival rates were calculated using the method of Kaplan and Meier. A statistical analysis was performed using the generalized Wilcoxon test and the log-rank test.

Results

Patient characteristics

The characteristics of the patients are shown in Table 2. Of the results from 117 patients, those of the 15 who received radiation therapy combined with L-TACE are analyzed elsewhere, and a total of 102 cases are analyzed in this report, including the 75 patients with HCC, the 12 patients with metastatic liver cancer treated with L-TACE, and the 15 patients with HCC who had a hepatic resection after L-TACE. The patients were divided into five groups according to the number of segments affected by tumors. The patients who had complications of cirrhosis were classified into groups A, B and C according to Child's criteria. The patients who had a hepatic resection demonstrated better liver functions. At the time of the analysis, 59 patients were still alive, but 43 had already died.

Change in the tumor size after L-TACE

The effects of L-TACE on the tumor size were examined according to the reduction rate of the tumor (Table 3). The reduction rate was calculated as described in the legend. The therapeutic responses were classified into four groups according to the reduction rate. Only the patients classified as showing partial response (PR) were considered to have responded effectively to the therapy. The effective rate was 22% for the HCC patients and 42% for the metastatic liver cancer patients.

Changes in the AFP levels after L-TACE

The changes of the levels of serum AFP were examined in 63 HCC patients (Fig. 1). The levels decreased one week after L-TACE in all the cases except four. 46 patients

Table 2. The characteristics of the patient population^a

Characteristic	HCC (L-TACE)	Metastasis	HCC (L-TACE + resection)
<i>n</i>	75	12	15
M:F	65:10	5:7	14:1
Age (years)			
mean	56.3	56.6	60.9
range	35~82	35~80	37~71
H ^b			
S	8	2	5
1	15	2	3
2	30	1	3
3	14	3	2
4	6	4	2
?	2		
Cirrhosis (–)	9		3
Cirrhosis (+)			
Child criteria ^c			
A	28		9
B	25		3
C	13		0
Alive	41	6	12
Dead	34	6	3

^a The patients were divided into HS–H4 according to the number of segments affected by tumors

^b HS, one subsegment; H1, one segment; H2, two segments; H3, three segments; H4, more than three segments

^c The patients with complications of cirrhosis were classified into A, B and C according to Child's criteria

Table 3. The therapeutic response to L-TACE

Response ^a (%)	Diagnosis (cases)	
	HCC (75)	Metastasis (12)
PR	13 (21.7%)	5 (41.7%)
MR	8 (13.3%)	2 (16.7%)
NC	25 (41.7%)	2 (16.7%)
PD	14 (23.3%)	3 (25.0%)
ND	15	0
Effective rate	21.7%	41.7%

^a The therapeutic responses were classified into four groups according to the reduction rate: PR (partial response) means that the reduction rate was more than 50% after therapy; MR (minor response) means that the rate was between 25% and 50%; NC (no change) means that the rate was 0%, and PD (progressive disease) means the tumor increased in size by more than 25%

The reduction rate (%) = $(A \times B - a \times b) \times 100 / A \times B$; where *A* was the longest diameter of the tumor measured on film during the imaging procedure, and *B* was the diameter measured at right angles to *A*. *A* and *B* were measured before therapy and *a* and *b* after therapy

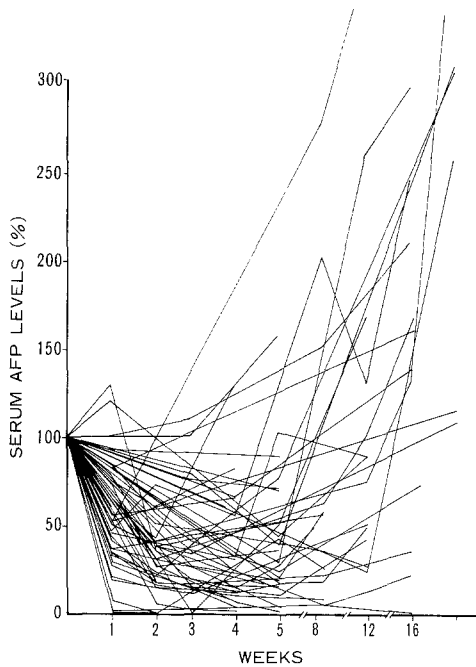
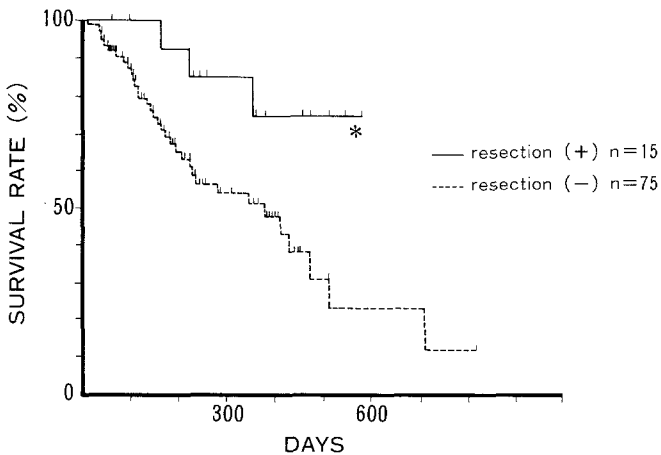


Fig. 1. The changes in the serum α -fetoprotein levels after L-TACE in 63 HCC patients. The value before therapy was assumed to be 100% and the changes after therapy were seen until 16 weeks after L-TACE

(73%) out of the 63 showed a more than 50% reduction. In some patients, the levels rose again between 5 and 16 weeks after therapy.

Survival rates

The cumulative survival rates after L-TACE are shown in Figs. 2, 3 and 4. The survival curves of the HCC patients who had a tumor resection after L-TACE show much better results than those for patients who had had no operation, and the difference was statistically significant ($P < 0.05$) (Fig. 2).



* $P < 0.05$

Fig. 2. The survival curves of the HCC patients treated with L-TACE with or without hepatic resection. The difference was statistically significant ($P < 0.05$)

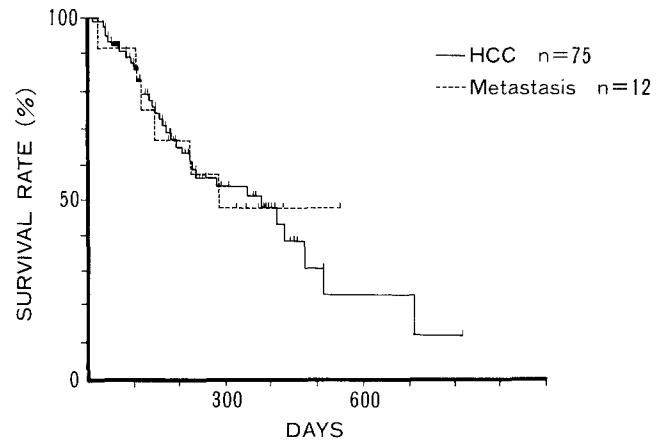


Fig. 3. The survival curves of the HCC and metastatic liver cancer patients treated with L-TACE. There was no statistically significant difference between both groups

Fig. 3 shows a comparison of the survival curve of HCC patients treated with L-TACE and that of metastatic liver cancer patients. Although the median survival period was 367 days for the HCC patients, and 268 days for the metastatic liver cancer patients, there was no statistically significant difference between the two groups.

Fig. 4 shows the survival curves of the HCC patients who were administered 5-fluorouracil tablets after L-TACE and those who were not. These two groups were not randomized. The original protocol required us to prescribe 5-fluorouracil tablets, but in fact some patients did not take the tablets for various reasons. We did not omit those cases and the results are illustrated in the figure. The median survival period was somewhat different, but there was no statistically significant difference between the two survival curves.

Side-effects

After L-TACE, no serious complications were recorded, but some side-effects were noted transiently. The major side-effects and their incidences are shown in Table 4. Fever was the most frequent symptom, followed by appetite loss, abdominal pain and nausea.

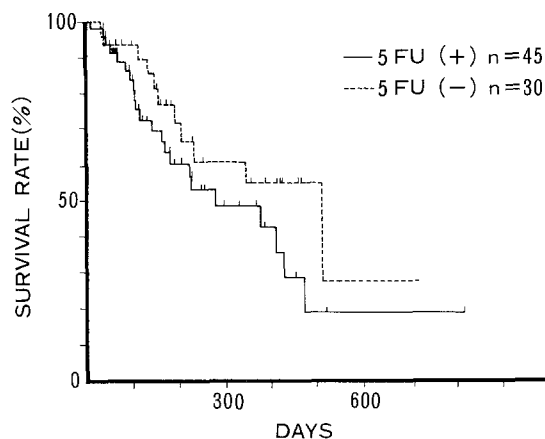


Fig. 4. The survival curves of the HCC patients treated with L-TACE, followed in some cases by oral administration of 5-fluorouracil. There was no significant difference between the groups

Table 4. The side-effects after L-TACE

Symptoms	Positive/total	Incidence
Appetite loss	17/80	20.5%
Nausea, vomiting	6/78	7.7%
Local pain	13/77	16.9%
Fever	27/83	32.5%

The changes in the blood chemistry and white blood cell count were noted 1 week after L-TACE, but they returned to their former levels within 4 weeks. There were no significant changes in the values of albumin and cholesterol (Fig. 5).

Discussion

This co-operative study was characterized by the participation of 20 national hospitals throughout Japan, using the same therapeutic protocol considered best for the treatment of patients with non-resectable hepatic neoplasmas.

The immediate therapeutic effects of L-TACE were first detected in the changes of the levels of serum AFP in the HCC patients. The levels dropped within one week after L-TACE, and 73% of the patients showed a more than 50% reduction compared with the former levels. These data demonstrated that L-TACE had the effect of immediately damaging HCC. In some patients, the AFP levels rose again over the former levels 5–16 weeks after L-TACE. For such cases, repeated L-TACE should be considered as a means of further damaging the tumor.

The effects of L-TACE were investigated by examining the survival rates. According to previous reports, the survival rates were 50% for about 9 months after TAE for HCC patients [3], or 44% for one year for 120 non-resectable HCC patients [6]. The median survival period of 367 days for our 75 HCC patients treated with L-TACE was a better result compared to those of previous reports. The

one-year investigation period was not enough to evaluate the prognosis of the patients, and the survival rates could be extended further with a follow-up study of our patients.

The response to chemotherapy for malignancy is usually evaluated by the reduction rate of the tumor size. The best response is classified as complete (CR) when the tumor disappears and no new tumors develop. In our study, there were no patients who could be classified as showing complete response, but 22% of the HCC patients and 42% of the metastatic liver cancer patients achieved a partial response. Although the response rate in the HCC patients was lower than that in the metastatic liver cancer patients, there was no difference between the survival rates of the two groups, and the levels of serum AFP were immediately lowered in most of the HCC cases after L-TACE. It has been reported that HCC shows coagulation necrosis after TAE, which makes the tumor size smaller, but hardly ever makes it disappear [1, 5]. It has also been reported that the low-density area of HCC is still detected by computerized tomography even after no tumor vessels are observed in angiography [6]. These results suggest that the HCC tumors have a tendency to maintain their size even after they have fully respond to therapy. The reduction rate might therefore be an inappropriate method of evaluating the effects of L-TACE on HCC.

The HCC patients who had a hepatic resection showed a better prognosis than those who had not (Fig. 2). On the basis of Table 2, the better liver functions of the resected patients would account for the better survival rates. However, even if only the patients in Child category A are compared, the survival rates of patients with hepatectomy were still better than those who had not undergone an operation (data not shown). In this regard, the preliminary analysis of the HCC patients without a hepatic resection, patients without cirrhosis ($n = 9$) and those with cirrhosis classified in category A ($n = 28$) demonstrated significantly better survival rates than those in category C ($n = 13$) up to 400 days after L-TACE (data not shown). However, there was no significant difference in the survival rates among the groups divided according to HS-H4 (data not shown). It is likely that the HCC patients with better liver functions showed a better prognosis after L-TACE.

Fig. 4 shows that the prognosis for HCC patients did not change as a result of the oral administration of 5-fluorouracil. However, a preliminary analysis of the 28 cases who lived for more than 100 days revealed that the 8 patients who had taken more than 20 g 5-fluorouracil showed a better prognosis than the 20 patients whose dose did not reach 20 g (data not shown). A further study will be needed to evaluate the effects of 5-fluorouracil.

The side-effects of L-TACE were the same as those of TAE reported previously [6], and were not serious, in spite of the fact that lipiodol and adriamycin had been additionally introduced. The influence of L-TACE on the liver function tests was minor and transient.

L-TACE is considered a safe and effective therapy for hepatic neoplasmas. Repeated L-TACE is to be considered in some cases, while the effects of oral chemotherapy after L-TACE need further investigation.

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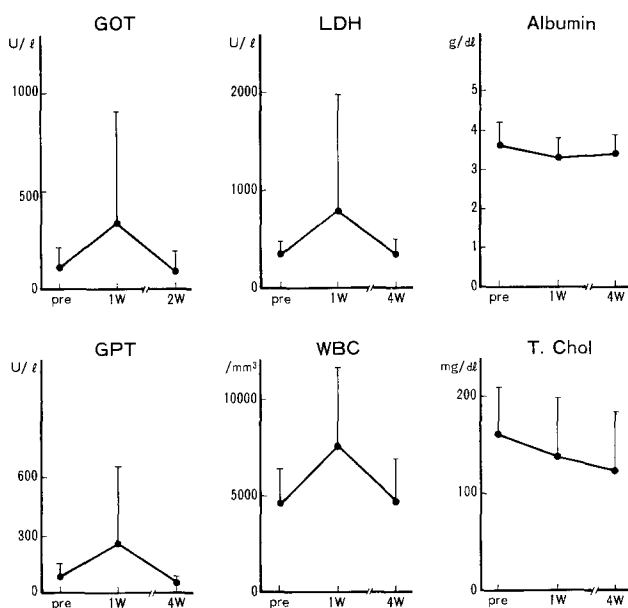


Fig. 5. The changes in the laboratory data after L-TACE treatment of the HCC patients

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