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Cooperative study on arterial regional chemotherapy for primary liver cancer in Hokkaido

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Summary. The Liver Study Group of Hokkaido analyzed a total of 57 patients with non-resectable primary liver cancers, which were treated by intra-arterial adriamicin infusion chemotherapy combined with lipiodol and/or the Gelform embolization of the hepatic arteries. Of the ten patients considered clinical responders, three complete response patients and seven partial response cases were obtained. The overall response rate was 17.5%. The median survival period at each clinical stage was as follows: stage I: 13.0 months, stage II: 16.0 months, stage III: 11.5 months and stage IV: 4.7 months. The common side-effects of this treatment were nausea, vomiting and anorexia. Hematological toxicities were also found, but there was no patient who suffered from severe complications.

Introduction

The recent development of diagnostic procedures, such as computerized tomography and ultrasonography, has enabled us to detect at an early stage liver cancers that indicate the need for a radical operation, while resectability has been gradually elevated. However, in Japan, there is a high incidence of liver cancer in association with liver cirrhosis, which restricts a hepatectomy even if the cancer is detected at an early stage.

For these reasons, resectability is at most around 30%, while a long prognosis is still unsatisfactory [2]. Thus, at present, there are more than a few hepatoma patients who have to undergo palliative therapy.

For the palliative treatment of liver cancers, including that of recurrent tumors after surgery, several kinds of therapeutic methods, such as ligation or the embolization of hepatic arteries, intra-arterial or systemic chemotherapy, and their combinations, have been widely employed over the past two decades.

To make an assessment of the efficacy of these forms of treatment, an analysis of a large number of patients is mandatory. The Cooperative Study Group on Liver Cancer in Hokkaido, Japan's most northern island, was organized about 5 years ago. The present report describes our clinical experience and evaluation of the efficacy of the treatment of advanced liver cancers in Hokkaido, especially the efficacy of adriamycin-containing chemotherapy for non-resectable primary liver cancers.

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Materials and methods

When we started this study, we employed three adriamycin-containing chemotherapy regimens (Table 1), but these regimens could be freely selected and the patients had a strong bias towards Arm-A, so the results of regimen A are mainly mentioned here.

In Arm-A, 20–50 mg/m^2 adriamycin were dissolved in a lipid contrast medium, lipiodol, and administered intra-arterially, followed by hepatic arterial embolization using Gelfoam or Ivaron, which were freely selected depending on the patient's liver functions.

During the two years from 1980, 76 cases of primary liver cancer came under this study, although five cases were excluded as ineligible for evaluation (Fig. 2). Fourteen resectable cases under adjuvant chemotherapy were used as references for a comparison of the survival period of the non-resectable cases.

The response criteria were defined by CT or US as follows: complete response (CR), the disappearance of all measurable tumors for at least 1 month; partial response (PR), a regression of more than 30% in the area of a measurable tumor for at least 1 month; no change (NC), a decrease or increase of less than 25% in the initial tumor lesion; progressive disease (PD), a 25% or greater increase in tumor size. The survival rates were calculated using the Kaplan-Meier method.

Results

The present study covered of a total of 57 patients with non-resectable primary liver cancer. 48 male and 4 female (Table 2), the preponderance of male patients was noted. Their ages ranged from 39 to 74 years and half of our patients were in their 50s. Thirty-one of the 57 patients were

Table 1. Dose schedule[a]

Regimen	Dosages
Arm-A	20–50 mg/m² i.a. (in Urografin) Adriamycin with lipiodol or/and Gelfoam (Ivalon)
Arm-B	CDDP 50–100 mg/m² i.a. Adriamycin 20–50 mg/m² i.a. (in Urografin) with lipiodol or/and Gelfoam (Ivalon)
Arm-C	10 mg/patient/day i.a. 1 → 14 days q. 4 weeks

[a] As more patients chose Arm-A, these results are mainly described

Table 2. Patient characteristics

Characteristic		Resectable case: treatment regines			Non-resectable case: treatment regines	
		A	B	C	A	B
Sex	M	9	2	1	48	5
	F			2	4	
Age	39>	1	1		2	1
	40–	1			9	
	50–	6		1	22	
	60–	1	1	1	12	4
	70<			1	7	
HBs·Ag	+	2	1		18	1
	–	1	1		25	4
	unknown	6		3	19	
Cirrhosis	+	8	1	3	31	4
	–	1	1		17	1
	unknown				4	
Stage[a]	I	6		3	6	1
	II	2			15	1
	III	1	1		8	
	IV				19	2
	unknown		1		4	1
Child	A	4	2	3	17	1
	B	5			16	1
	C				7	2
	unknown				12	1
Total		9	2	3	52	5
		14			57	

[a] Clinical stages according to the general rules of the Liver Study Group of Japan. Stage I, T1, N0, M0; stage II, T2, N0, M0; stage III, T3, N0, M0, or T1–3, N1, M0; stage IV, T4, N1, M0s or T1–4, N0, M1, T1, a solitary tumor 2 cm or less in its greatest dimension without vascular invasion; N0, no regional lymph node metastasis; M0, no distant metastasis

Table 3. The responses of the non-resectable cases when the response rates are compared between the patients who had received the one course treatment and those who had received treatment of more than two courses

Response	No. of cases		Total
	1 course	2 courses <	
CR	0	3	3
PR	1	6	7
NC	16	18	34
PD	8	5	13
Response rate	1/25 4.0%	9/32 28.1%	10/57 17.5%

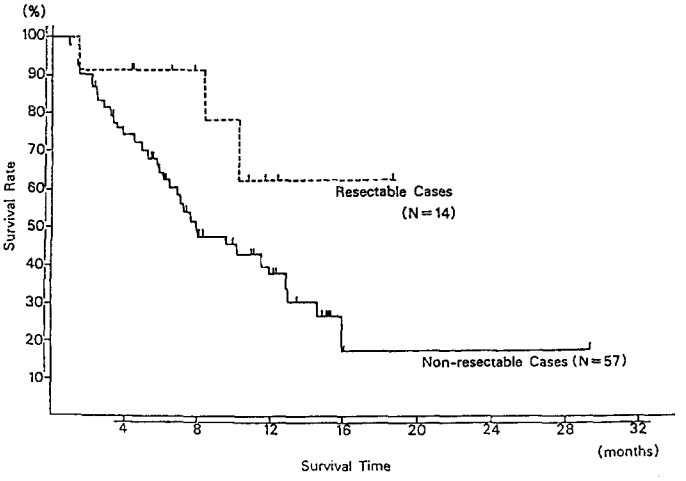

Fig. 1. Survival rates (resectable vs non-resectable). The apparent differences in the survival rates of the two groups were observed

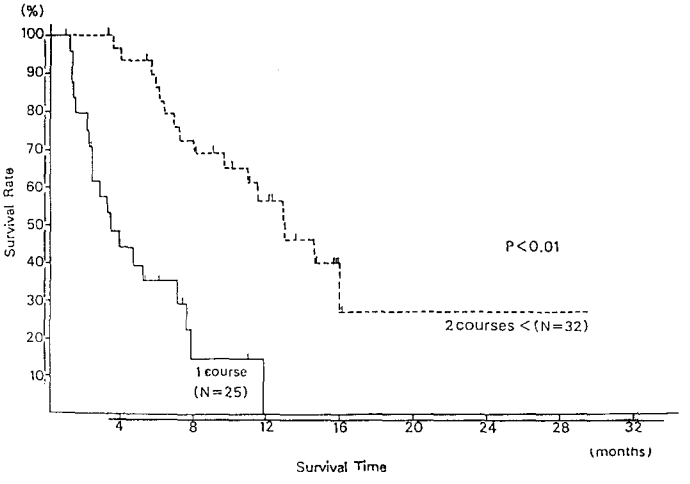

Fig. 2. Survival rates (number of treatment courses: 1 vs 2 <)

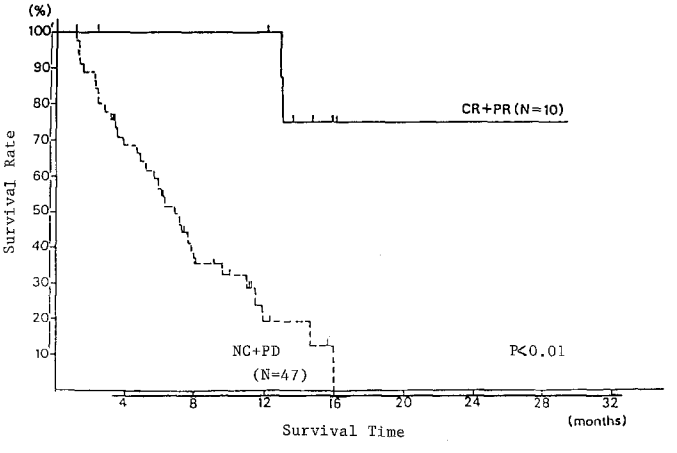

Fig. 3. Survival rates (responders vs non-responders)

Table 4. Responses of non-resectable cases when the response rates for each treatment are compared

Response	ADR+TAE[a]	ADR+lipiodol	i.a. one shot	Total
CR	0	3	0	3
PR	0	7	0	7
NC	11	22	1	34
PD	3	9	1	13
Response rate	0/14 0%	10/41 24.4%	0/2 0%	10/57 17.5%

[a] TAE, transarterial embolization; ADR, adriamycin

suffering from liver cirrhosis, while in 19 patients the HB antigens were positive. The Liver Cancer Study Group of Japan [2] divides the pathophysiological stage of primary liver cancer into four further stages depending on the tumor size, the number of liver tumors and the presence or absence of vascular invasion. The number of liver cancer patients at each stage and the Child classification are shown in Table 2.

When we compared the survival periods of the resectable and the non-resectable cases, there was an apparent 1-year difference in the survival rate (Fig. 1).

The overall response rate of the non-resectable cases was 17.5%. Nine out of the 32 patients who were able to undergo more than two courses of this treatment showed better results. The response rate was 28.1% (Table 3, Fig. 2).

The efficacy of the intra-arterial infusion of anticancer agents with lipiodol in cases of liver cancer has been gradually investigated in Japan. In this study, 10 patients out of the 41 who received adriamycin with lipiodol achieved CR or PR, but no response was obtained using other treatments (Fig. 3).

Comparing the survival rates of the responders and non-responders, the 1-year survival rate was 100% for the in responders, while the 2-year survival rate was estimated at around 75% (Table 4). On the other hand, for the non-responders, the 1-year survival rate was only 20% (Fig. 3). There were ten patients, nine male and one female, who were considered as responders (CR + PR) in the non-resectable cases (Table 5). Half of these patients were cases associated with liver cirrhosis, while four patients were positive for HB antigens. The survival periods ranged from 2.3 months to 29 months, which did not have a close correlation with the total dosage of adriamycin or other anticancer agents. As for the Child classification, three cases remained unknown, while the other seven patients belonged to A or B.

The survival rates of the patients with a solitary tumor and those with multiple tumors were also compared (Fig. 4). The patients with a solitary tumor had better survival rates statistically.

As for the survival rate at each clinical stage (Fig. 5), there was no statistical difference among patients at stages I, II and III, but there were differences observed between stages IV and I or II.

As regards the changes in the serum α-fetoprotein levels (Fig. 6), it was found that these values had lowered up to 2 weeks after treatment in both the CR + PR and NC + PD groups, but a tendency toward the re-elevation of the serum α-fetoprotein levels was detected in the NC + PD group.

The side-effects of this treatment (Table 6), such as fever, nausea, vomiting and anorexia, were often observed, but most of these were temporary. They may have been due to the hepatic arterial embolization or injection of the oily lipiodol fluid, but not to the administration of adriamycin.

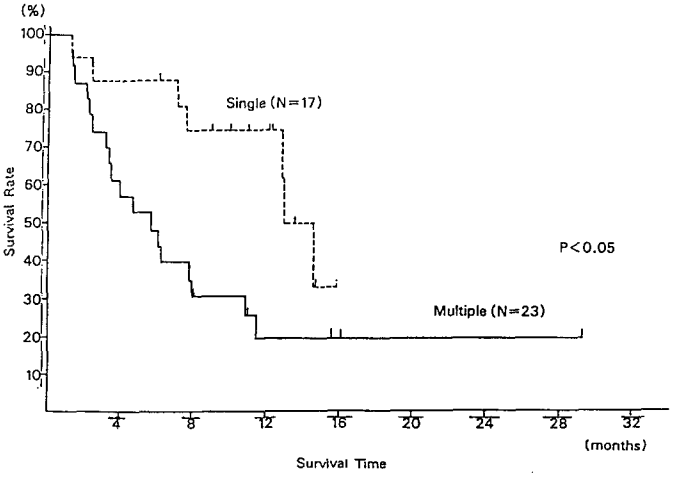

Fig. 4. Survival rates (number of tumors: solitary vs multiple tumors). The statistical differences in the survival rates between the two groups were observed

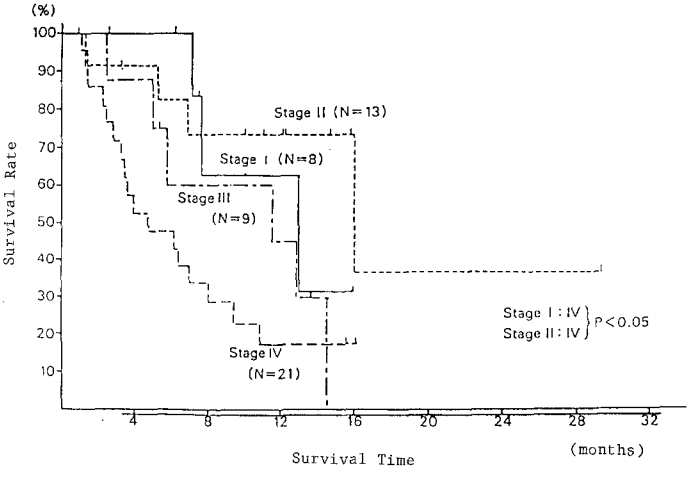

Fig. 5. Survival rates (clinical stage). There was no difference between stages I, II and III. The survival rates at stage IV were very poor

Table 5. Responders in non-resectable cases

No.	Sex	Age	Stage	Cirrhosis	Child	HBs·Ag	Adriamycin, total dose (mg)	Response	Survival time (months)
1	M	52	II	+	?	−	90	CR	15.8 alive
2	M	47	II	+	B	+	120	CR	14.7 alive
3	F	71	III	−	B	−	90	CR	13.6 alive
4	M	48	II	+	A	−	170	PR	29.3 alive
5	M	43	IV	−	?	+	180	PR	16.1 alive
6	M	69	I	−	A	−	160	PR	15.9 alive
7	M	56	I	−	B	+	60	PR	13.0 dead
8	M	49	III	+	B	+	60	PR	12.9 dead
9	M	54	II	+	A	−	40	PR	12.1 alive
10	M	52	II	−	?	−	30	PR	2.3 alive

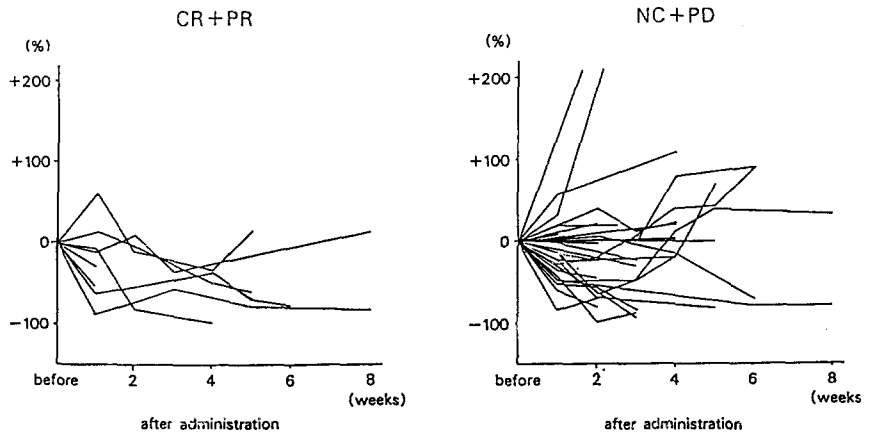

Fig. 6. Changes in the α-fetoprotein levels. The percentage α-fetoprotein values (before/after treatment × 100) were plotted

Table 6. Side-effects

Side-effects	No. of cases (%)
Alopecia	0/32 (0)
Stomatitis	1/32 (3.1)
Nausea/vomiting	11/37 (29.7)
Fever	18/44 (40.9)
Hematological toxicity	12/87 (13.8)
Tachycardia	2/34 (5.9)
Anorexia	13/36 (36.1)

Discussion

To know the natural course of liver cancer is a prerequisite in the assessment of the effectiveness of treatment. Nagasue [3] reported that the mean survival period for the total number of patients was 4 months from the onset of the initial symptoms to death. Okuda [4] also described the natural course of hepatocellular carcinoma, in which the median survival period from diagnosis of 169 untreated patients with primary liver cancer was 1.6 months.

From our clinical results, the mean survival period for the total number of 57 non-resectable cases in this study was 7.9 months, and very favorable results are obtained if we compare the natural course of primary liver cancer.

Quite a number of papers have supported the efficacy of the intra-arterial infusion or embolization of the hepatic arteries that nourish liver tumors. It is quite rational to deliver anti-cancer agents to the liver tumors via the hepatic arteries or to embolize these arteries. Especially in liver cell carcinoma, the blood supply to the tumor is almost exclusively from the hepatic artery. However, it is commonly recognized that the rapid development of collateral vessels and the recanalization of the embolized hepatic arteries after treatment interfere with their therapeutic effectiveness. However, these difficulties have been overcome by selective drug targeting therapy on liver tumors using the oily contrast medium, lipiodol. In this study, our ability to obtain rather long survival periods can be explained by the fact that the therapeutic response of the initial treatment with adriamycin in lipiodol was very intensive. This might therefore be responsible for the long survival periods. Naturally, long-term maintenance therapies, such as the re-embolization of the hepatic arteries and the continuous or intermittent intra-arterial infusion of anti-neoplastic agents should not be ignored as a means to obtain a better prognosis.

The median survival period for stage IV was quite poor, being only 4.7 months, which was nearly the same as the survival periods of patients who had gone through the natural course of liver cancer. This fact suggests that careful consideration should be paid when we decide on the type of treatment for patients at stage IV.

From our results, it can be concluded that, at present, the intra-arterial adriamycin infusion chemotherapy combined with lipiodol is the most effective treatment for non-resectable liver cancer. Although the efficacy of additional hepatic arterial embolization was not recognized in this study, it cannot be denied that there is a necessity for maintenance therapy with a series of trial treatments to obtain a more favorable prognosis.

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