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Significance of multidisciplinary therapy for hepatocellular carcinoma*

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Summary. The effect of multidisciplinary therapy for hepatocellular carcinoma (HCC) was evaluated in 121 resected cases. The 5-year survival was 100% for absolute curative resection (12 cases), 59.1% for relative curative resection ($n = 37$) and 10.9% for relative non-curative resection ($n = 59$). However, none of the patients survived for more than 3 years after absolute non-curative resection ($n = 13$). The non-recurrence in the preoperative TAE groups was different from that in non-TAE groups undergoing absolute and relative curative resection. The 1- and 3-year non-recurrence rates for relative non-curative resection were 92.3% and 53.8%, respectively, for the preoperative TAE group and 56.1% and 28.1%, respectively for the non-TAE group. These data show that preoperative TAE is effective in relative non-curative resection. Functional disturbances of the coagulation-fibrinolysis system in cirrhotic patients were improved after PSE. All patients undergoing hepatectomy after PSE had an uneventful postoperative course, including well-maintained function of the coagulation-fibrinolysis system and a decrease in splenic volume. At 1 year after hepatectomy, cirrhotic patients with critical liver function and poor coagulation-fibrinolysis showed appreciable hepatic regeneration. One patient died of hepatic failure 1 year after the operation. In recurrent HCC, the 1-, 2- and 3-year survivial values after reresection were 100%, 75.0% and 25.0%, respectively. The respective values following TAE were 79.0%, 42.0% and 9.0%. Three cases of recurrent HCC were effectively treated, i.e., two patients achieved a partial response and one showed no change, by continuous intra-arterial infusion of 5-FU and lentinan with intermittent one-shot injections of epirubicin using a subcutaneous infusion pump. These three patients are alive at 1 year and 7 months, 1 year and 4 months and 6 months after the treatment, respectively.

Introduction

Hepatocellular carcinoma (HCC) is the most malignant digestive tract tumor. Recently, the resectability rate has increased to over 50% [5] due to advances in the imaging modalities and operative procedures for HCC. However, the recurrence rate remains high, and the long-term survival of resected patients is unsatisfactory. Multidisciplinary therapy for HCC is very important for improvement of the prognosis. Therefore, we evaluated the effects of multidisciplinary therapy for HCC in 121 resected cases.

Patients and methods

Of the 216 cases of HCC treated at Mie University during the last 13 years and 7 months, 121 resected cases, including 101 cases associated with liver cirrhosis, were retrospectively analyzed (Table 1).

The effects of preoperative transcatheter arterial embolization (TAE), chemolipiodolization after surgery and preoperative partial splenic embolization (PSE) were evaluated. The modes of therapy for recurrent cases, including reresection, repeated TAE and the continuous intra-arterial infusion method using a subcutaneous infusion pump were also reviewed.

The clinical and pathological findings were classified according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan [6]. Absolute curative resection is defined as liver resection TW(–) (no macroscopic cancerous infiltration within 10 mm of the cut liver surface in freshly excised specimens) in stage I disease (Tables 2, 3). Relative curative resection is defined as liver resection TW(+), with tumor tissue being removed, in stage I disease or as liver resection Hr>H, R>N, TW(–) in stage II or III disease. In either case, no residual tumor embolus appears in the portal vein or bile duct on images of the remaining liver (Tables 2, 3).

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Table 1. Hepatocellular carcinoma

Operation	Number of cases	Liver cirrhosis	
		(+)	(–)
Resection	121 (56.0%)	101 (56.4%)	20 (54.1%)
Ligation of vessels	16	12	4
Infusion	8	5	3
Others	2	1	1
Inoperable	69	60	9
Totals	216	179 (82.9%)	37

Table 2. General Rules for the Clinical and Pathological Study of Primary Liver Cancer – macroscopic staging [6]

T factors:
- T1: A single tumor measuring 2 cm or less in its greatest dimension, no vascular invasion
- T2: A single tumor measuring 2 cm or less in its greatest dimension, vascular invasion
  Multiple tumors with a maximal diameter of 2 cm or less, confined to one lobe
  A single tumor with a diameter exceeding 2 cm, no vascular invasion
- T3: A single tumor with a diameter exceeding 2 cm, vascular invasion
  Multiple tumors with diameters exceeding 2 cm, confined to one lobe
- T4: Multiple tumors in more than one lobe
  Associated vascular invasion in the first branch of the portal or hepatic vein

N factors:
- N0: No metastasis in group 1 lymph nodes[a]
- N1: Metastasis in at least group 1 lymph nodes

M factors:
- M0: No distant metastasis
- M1: Distant metastasis

Stage	Factor		
	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1–T3	N1	M0
IVA	T4	N0–1	M0
IVB	T1–T4	N0–1	M1

[a] Group 1 lymph nodes:
a. Subdiaphragmatic lymph nodes of the upper region of the liver
b. Lymph nodes in the hepatic porta

Results

Survival of resected cases

Operative death occurred in 5 (4.1%) of the 121 resected cases. The 3- and 5-year survival values were 60.1% and 39.4%, respectively, for all resected cases. The 5-year survival was 100% for absolute curative resection, 59.1% for relative curative resection and 10.9% for relative non-curative resection. However, no patients undergoing absolute non-curative resection survived for more than 3 years (Fig. 1).

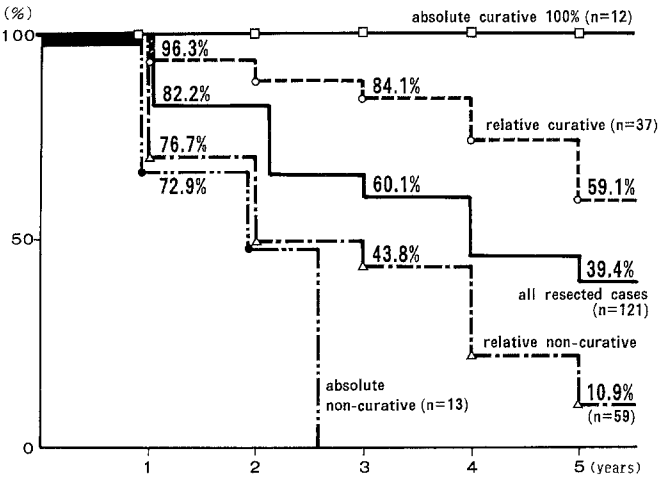

Fig. 1. Survival of hepatectomized cases (Kaplan-Meier)

Table 3. General Rules for the Clinical and Pathological Study of Primary Liver Cancer [6]

Extent of resection (Hr):
- Hr O: Resection of less than one subsegment
- Hr S: Resection of one subsegment
- Hr 1: Resection of one segment
- Hr 2: Resection of two segments
- Hr 3: Resection of three segments
- Hr 4: Resection of four segments

Extent of lymph node dissection (R):
- R_0: Liver resection with no dissection or incomplete dissection of group 1 lymph nodes
- R_1: Liver resection with dissection of group 1 lymph nodes
- R_2: Liver resection with dissection of Group 1 and confirmed group 2 lymph nodes

Macroscopic classification (TW):
- TW(–): No macroscopic cancerous infiltration within 10 mm of the cut liver surface in freshly excised specimens
- TW(+): Macroscopic cancerous infiltration within 10 mm of the cut liver surface in freshly excised specimens

Effect of preoperative TAE

The 5-year non-recurrence rates in the presence and absence of preoperative TAE were 80.0% and 75.0% for absolute curative resection and 39.1% and 33.7% for relative curative resection, respectively. The differences were not significant. However, the 2-year non-recurrence rates in the presence and absence of preoperative TAE were 56.1% and 28.1% for relative non-curative resection and 83.3% and 33.3% for absolute non-curative resection, respectively. These differences were significant (Fig. 2).

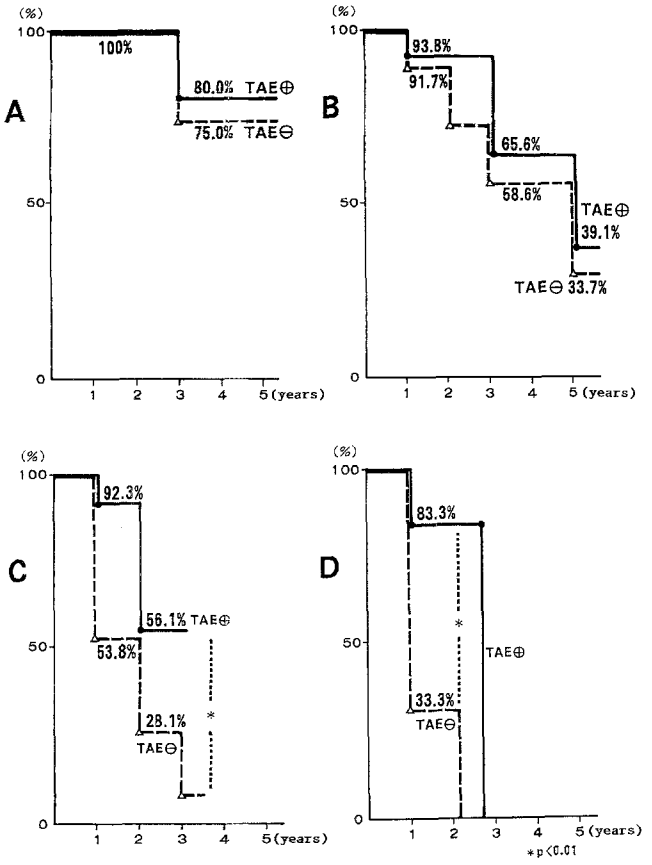

Fig. 2 A–D. Preoperative TAE and non-recurrence rates in hepatectomized cases (Kaplan-Meier). **A** Absolute curative resection. **B** Relative curative resection. **C** Relative non-curative resection. **D** Absolute non-curative resection

Partial splenic embolization

In investigations of the preoperative function of the coagulation-fibrinolysis system, eight parameters were examined as prognostic factors and evaluated as being positive as follows: a platelet count of less than 60,000/mm^3, a PT value below 70%, an APTT value above 40 s, a fibrinogen level below 150 mg/dl, an FDP value above 10 μg/ml, an Ma value below 30 mm, an Ma/K value of less than 2.0 as determined from a thromboelastogram, and an AT-III value below 50%. The risk of preoperative disseminated intravascular coagulation (DIC) in cirrhotic patients must be considered when more than five of these eight parameters are positive.

Partial splenic embolization (PSE) was performed in 13 patients with severe functional disturbances of the coagulation-fibrinolysis system associated with liver cirrhosis. In these 13 patients, the mean number of positive risk factors for DIC decreased from 3.6 to 1.0 within 4 weeks after PSE, indicating marked improvement in the function of the coagulation-fibrinolysis system. Improvement of the liver function manifesting as a change from a total risk [7] of 4 to a total risk of 3 was observed in two patients, and an enhancement of residual liver function Rmax [7] was noted in one case (patient 8). All patients who underwent PSE, including six cases at risk for DIC, had an uneventful postoperative course, including well-maintained function of the coagulatiton-fibrinolysis system, a decrease in splenic volume at 1 year after hepatectomy and appreciable hepatic regeneration. Indicating that preoperative PSE was very effective in patients with severe functional disturbances of the coagulation-fibrinolysis system associated with liver cirrhosis (Table 4).

Table 4. Results of hepatectomy after PSE

Patient Number	Age (years)	Sex (M/F)	Total risk			Positive risk factors for DIC			Operation	Outcome	
			Before PSE	⇨	After PSE	Before	⇨	After			
1	53	F	4	⇨	4	7	⇨	2	S_7	5 years and 3 months	Alive
2	39	M	4	⇨	3	5	⇨	1	Anterior	3 years and 10 months	Alive
3	58	M	4	⇨	3	6	⇨	1	Anterior	3 years and 6 months	Alive
4	65	F	4	⇨	4	5	⇨	1	Partial	2 years and 10 months	Alive
5	56	M	3	⇨	3	4	⇨	1	Anterior	2 years and 3 months	Alive
6	53	M	4	⇨	4	6	⇨	2	Partial	2 years and 1 months	Alive
7	51	M	4	⇨	4	6	⇨	2	S_8	1 year	Dead[a]
8	51	M	4	⇨	4	0	⇨	0	S_8	1 year and 8 months	Alive
9	66	F	4	⇨	4	3	⇨	2	Partial	1 year and 6 months	Alive
10	55	M	2	⇨	2	3	⇨	2	Right	8 months	Alive
11	57	M	2	⇨	2	1	⇨	0	S_3	5 months	Alive
12	50	M	3	⇨	3	3	⇨	0	S_8	4 months	Alive
13	60	F	3	⇨	3	1	⇨	0	S_8	4 months	Alive
Average			3.4±0.8		3.2±0.8	3.6±2.2		1.0±0.8			
			NS			$P<0.01$					

[a] Liver failure

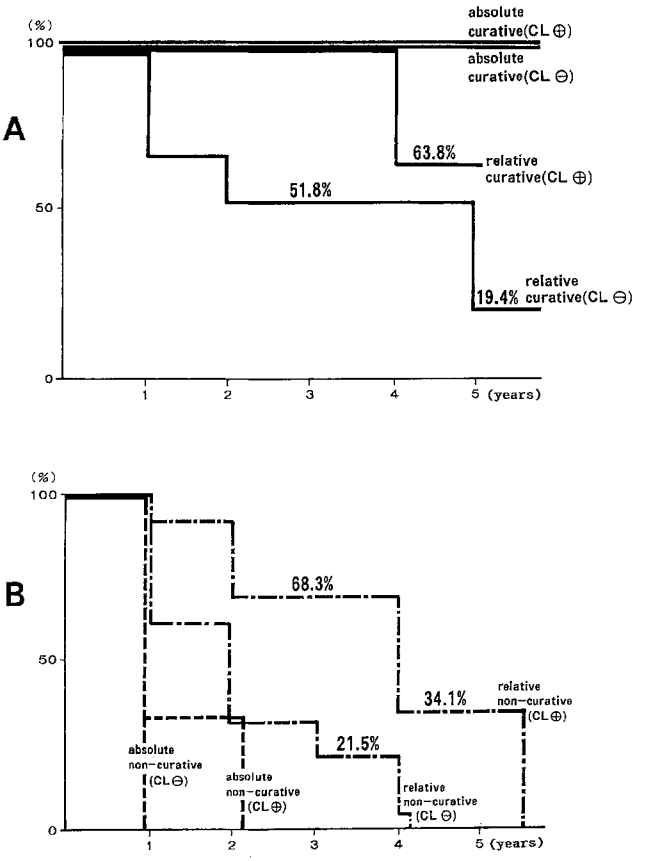

Fig. 3 A, B. Postoperative chemolipiodolization (*CL*) and survival of hepatectomized cases (Kaplan-Meier). **A** Curative resection. **B** Non-curative resection

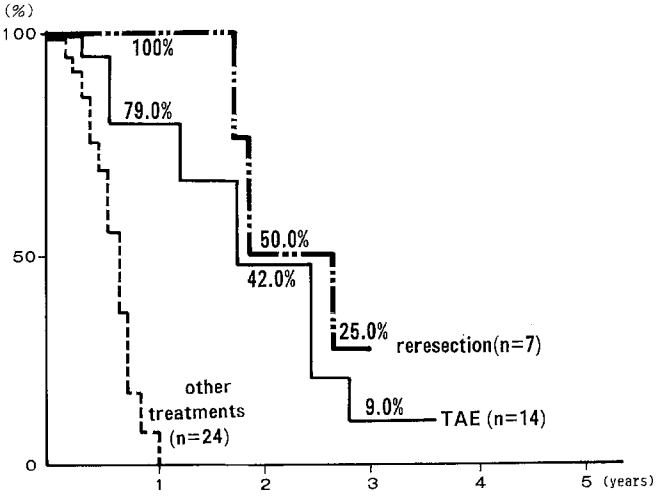

Fig. 4. Effect of reresection and TAE for recurrent cases after operation (Kaplan-Meier)

Treatment after hepatectomy

At 1 month after hepatectomy, chemolipiodolization (CL) was performed in 30 patients. The 5-year survival values were 63.8% and 19.4% in the presence and absence of CL, respectively, for relative curative resection. The 5-year survival in the presence of CL was 34.1% for relative non-curative resection, whereas none of the patients undergoing relative non-curative resection in the absence of CL survived for more than 5 years. Postoperative chemolipiodolization was thus very effective, especially in the relative non-curative group (Fig. 3).

Therapy for recurrent cases

Reresection. Seven reresections were performed for intrahepatic solitary recurrences, including repeated resection in one patient, transthoracic reresection in one subject and simultaneous reresections of both liver and lung recurrences in two cases. One patient has survived for 6 years and 5 months after the first hepatectomy (Table 5).

TAE. None of the 24 patients who did not undergo TAE survived for more than 1 year after recurrence. However, the 1-, 2- and 3-year survival values after recurrence were 79.0%, 42.0% and 9.0%, respectively, in 14 patients undergoing repeated TAE. Repeated TAE was thus effective in recurrent cases (Fig. 4).

Continuous intra-arterial infusion using a subcutaneous infusion pump. Continuous intra-arterial infusion of 5-FU and lentinan (a purified polysaccharide of 1-3-D-glucan isolated from *Lentinus edodes*, Tokyo, Japan) with intermittent one-shot injection of epirubicin (10 mg) using a subcutaneous infusion pump was performed for one preoperative, six prophylactic, four recurrent and three reduction surgery cases.

Microscopically, intrahepatic metastasis, vascular invasion and capsular infiltration were observed in the prophylactic group, and the risk of recurrence was considered to be high. Therefore, these cases were treated prophylactically by continuous intra-arterial infusion therapy. All patients are presently alive and show no sign of recurrence.

Four recurrent cases were treated by continuous intra-arterial infusion therapy. Two patients who underwent subsegmentectomy had recurrent tumors in the remaining liver, one occurring at 2 years and one, at 2 years and 6 months after the subsegmentectomy. TAE and/or subcutaneous enthanol injection therapy was performed. However, due to enlargement of the recurrent tumors, continuous intra-arterial infusion therapy was carried out. A partial response (PR) was observed in two patients, who have survived for 1 year and 11 months and for 1 year and 4 months, respectively, since the start of this therapy. In the third patient, the HCC mass was large (16 cm in diameter) and very advanced; a right trisegmentectomy was performed. At 4 months after surgery, recurrence was detected in the remaining liver. Intra-arterial continuous infusion therapy was initiated. Neither an enlargement of the residual tumor nor the appearance of a new tumor has been observed. This patient has survived for 8 months since the recurrence (Table 6).

Discussion

Due to recent progress in imaging modalities and to the establishment of new tumor markers, the diagnosis of HCC

Table 5. Results of resection with hepatectomy for recurrence after the first hepatectomy

Case, age (in years), sex (M/F)	LC	Hepatectomy					Survival	
		First		Second		Third	After hepatectomy	After first hepatectomy
1. 54 F	(+)		Recurrence at 2 years and 6 months after				3 years and 11 months	6 years and 5 months Alive
		S_6 partial	⇨	S_7 partial				
2. 56 M	(+)		Recurrence at 2 years and 10 months after		Recurrence at 1 year and 6 months after		2 years and 7 months	5 years and 5 months
		S_6 partial	⇨	TAE S_5 partial	⇨	TAE trisegment-ectomy	(1 year and 1 month)	Rupture of varices, dead
3. 53 F	(+)		Recurrence at 3 years and 6 months after				7 months	4 years and 2 months
		S_7 partial	⇨	Transthoracic S_5 partial				Alive
4. 58 M	(+)		Recurrence at 2 years and 10 months after				10 months	3 years and 8 months
		S_3	⇨	S_7 partial				Liver failure, dead
5. 50 M	(+)		Recurrence at 1 year and 8 months after		Recurrence at 6 months after		2 years and 2 months	3 years and 10 months
		S_5 partial	⇨	S_6	⇨	TAE		Dead
6. 53 M	(+)		Recurrence at 3 years and 1 month after			1 month		3 years and 2 months
		Lateral	⇨	S_5 partial, lung partial				Alive
7. 50 M	(+)		Recurrence at 1 year and 2 months after			6 months		1 year and 8 months
		S_6 partial	⇨	S_3 partial, lung partial				Alive

has become easier and the rate of detection of small liver cancers has increased. However, the resectability rate remains only slightly over 50% [5], and the survival of resected cases is not yet satisfactory. Therefore, multidisciplinary therapy is important for improvement of the survival not only of resected cases but also of unresectable cases.

The purposes of preoperative TAE are to decrease the size of the main tumor and to prevent invasion of the capsule, formation of tumor emboli in the portal vein and formation of intrahepatic metastasis. Although the necrotizing effect of TAE on the main tumor is satisfactory, its effect on invasion of the capsule and formation of tumor emboli in the portal vein or intrahepatic metastasis is weak. Yamazaki et al. [16] have obtained 3- and 5-year survival values of 65.7% and 39.4%, respectively, using preoperative TAE and respective values of 61.9% and 49.8% in the absence of preoperative TAE for all resected cases. They concluded that preoperative TAE was not effective. Fujiwara et al. [2] reached the same conclusion. On the other hand, Imaoka et al. [3] reported that the disease-free survival of patients who underwent preoperative chemoembolization using lipiodol, cisplatin and Gelfoam was better than that of patients who underwent preoperative chemoembolization using lipiodol, Adriamycin and Gelfoam. These authors recommended preoperative chemoembolization using lipiodol, cisplatin and Gelfoam as a useful method to prevent the recurrence of HCC after surgery. Preoperative TAE in relative non-curative resection improved the outcome in our cases, and we recommend preoperative TAE in cases of non-curative resection, especially in stages II and III.

Chemolipiodolization performed at 1 month after hepatectomy improved the survival and was a very effective prophylactic therapy. Lipiodol remains selectively in the tumor for a long time and in itself has a weak embolizing effect on the artery. TAE might cause liver failure and cannot be performed when the portal vein is obstructed. However, the liver damage induced by chemolipiodolization in our series of patients was mild. Therefore, chemolipiodolization should be carried out even in patients showing reduced liver function after hepatectomy. Kane-

Table 6. Effect of intra-arterial continuous infusion therapy using a subcutaneous infusion pump (reservoir) – recurrence

Case, age (in years), Sex (M/F)	Stage	Curability (resected area)	Duration to recurrence	Treatment for recurrence				Outcome after operation
				At detection	6 months	1 year	1.5 year	
1. 60 M	II	Relative curative (subsegment)	2 years			reservoir		3 years and 7 months
				TAE	TAE			
					PD	PR		Alive
2. 64 M	II	Relative curative (subsegment)	2 years and 6 months			reservoir		3 years and 10 months
				TAE, PEIT	TAE			
				PD		PR		Alive
3. 66 M	IVA	Relative non-curative (trisegment)	4 months	reservoir				1 year
				NC				Alive
4. 62 M	III	Relative non-curative (segment)	1 year and 9 months	TAE				6 months
				reservoir				
				PR				Alive

Reservoir: continuous intra-arterial infusion of 5-FU and lentinan (a purified polysaccharide of 1-3-D-glucan isolated from *Lentinus edodes*, Tokyo, Japan) with intermittent one-shot injection of epirubicin using a subcutaneous infusion pump. PEIT, Percutaneous ethanol injection therapy; PD, progressive disease; PR, partial response; NC, no change

matsu et al. [4] reported a marked decrease in serum alpha-fetoprotein levels and a decrease in the tumor size on hepatic imaging in 13 patients with primary HCC who had been treated with a lipiodol-Urografin system containing anticancer agents. Their histological investigations of resected specimens proved this mode of therapy to be effective in 10 of the 13 patients (77%). Chemolipiodolization was also found to be effective in our cases and was considered to be the most effective therapy in the early period after hepatectomy. This therapy has been used for the treatment of HCC after hepatic resection.

Percutaneous ethanol injection therapy (PEIT) [13–15] has been widely used for small liver cancers (<2 cm) in Japan because absolute ethanol destroys tumor tissue, mainly due to its dehydrating and protein degeneration effects and partly due to its thromboembolic effect. Ebara et al. [1] reported that the 1-, 3- and 4-year survival values for patients with tumors measuring less than 3 cm in diameter were 96%, 79% and 79%, respectively, following ethanol injection therapy. Histopathological examination revealed an area measuring at least 3 cm in diameter that was almost completely necrotic. However, in large tumors, it would be difficult to inject ethanol throughout the tumor. Furthermore, in such cases, intrahepatic metastasis frequently exists, even if it is not detected by imaging techniques. In addition the value of ethanol injection is limited in patients with multiple lesions.

Many patients develop severe disturbance of the coagulation-fibrinolysis system due to liver cirrhosis. Recognition of this pathophysiology is very important in the consideration of hepatectomy. In the present study, preoperative PSE was performed in patients with hypersplenism and severe disturbance of the coagulation-fibrinolysis system due to liver cirrhosis, and it resulted in improvement of the coagulation-fibrinolysis function. All 13 patients undergoing hepatectomy after PSE, including 6 at risk for DIC, had an uneventful postoperative course, showing well-maintained function of the coagulation-fibrinolysis system and a decrease in splenic volume, and they displayed appreciable hepatic regeneration at 1 year after hepatectomy. Preoperative PSE was thus very useful in HCC associated with severe disturbance of the coagulation-fibrinolysis system due to liver cirrhosis. In cases at risk for DIC, especially thrombocytopenia, PSE should be effective and should be performed.

Because many cases of recurrence were observed after hepatectomy, the treatment of recurrence in patients is an important problem. Nagasue et al. [9] performed a second hepatic resection in 9 of 31 patients with recurrent disease; 6 patients survived for 15–45 months after the first operation (4 being free of HCC and 2 showing residual disease). The survival of these 9 patients was significantly better than that of the 22 patients who were treated by other palliative methods. For our seven reresection cases, the 1- and 3-year survival values were 100% and 25.0%, respectively; the patient surviving the longest has been alive for 3 years and 11 months and show no sign of disease. Reresection is thus surmised to be a feasible and meaningful method of treatment for patients with recurrence in the remaining liver.

TAE is very effective in non-resectable recurrent tumors. However, liver damage, obstruction of the artery feeding the main tumor and neovascularization of collateral arteries have been noted following TAE. On the other hand, intra-arterial infusion therapy using a subcutaneous infusion pump is useful in the treatment of patients with severe liver dysfunction. Miura [8] reported that the tissue concentration of the drug was very high, i.e., 50 or sometimes 100 times higher, following intra-arterial infusion, and an objective response occurred in 50% of the patients. The outcome was satisfactory in patients who had undergone prophylactic, recurrent or reduction surgery followed by intra-arterial infusion therapy. Recently, adoptive immunotherapy such as LAK cell infusion into the hepatic artery has been performed, and the results of evaluation of its effect are now being eagerly awaited [10–12].

We conclude that for the absolute curative resection group, oral chemotherapy alone may be sufficient. For the relative curative resection group, postoperative chemolipiodolization or/and intra-arterial infusion therapy should be applied. For the non-curative resection group, intraoperative ethanol injection therapy, chemolipiodolization, continuous intra-arterial infusion therapy and/or TAE should be undertaken. Reresection should be performed if it is feasible on the basis of re-evaluation of the function of the remaining liver. Repeated TAE and/or continuous intra-arterial infusion therapy should be carried out if hepatic reresection is not indicated.

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