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New Indication for Reduction Surgery in Patients with Advanced Hepatocellular Carcinoma with Major Vascular Involvement

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Abstract

Background: The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly in patients with tumor thrombi (TT) in the major vessels.

Patients and Methods: From July 1992 to October 2004, 161 patients diagnosed as having advanced HCC with major vascular involvement were seen consecutively at our hospital. Among these patients, 32 (20%) underwent surgical resection [16 complete resection (CR), 16 reductive resection (RR)]. Eighteen patients (11%) received radiotherapy (RT), 73 (45%) underwent transcatheter arterial chemoembolization (TACE) or transcatheter arterial infusion chemotherapy (TAI), 8 (5%) with distant metastases received systemic chemotherapy, and 30 (19%) received palliative therapy.

Results: Excluding the CR group, the patients in the RR group had a higher 1-year survival rate than the other treatment groups. However, there was no significant difference in the overall survival rates of the RR, RT, and TACE/TAI groups. When we evaluated prognostic factors to clarify the indications for RR in the multidisciplinary treatment of patients with advanced HCC with TT, prothrombin activity (PA) was identified as a significant independent preoperative factor for overall survival in the RR group. The survival rate in patients with PA of ≤78% was significantly lower than that of patients with PA of >78% ($P = 0.0004$). The median survival time of patients with serum PA of >78% who underwent RR was 13.9 months and that of patients who underwent CR was 9.1 months, with no survival difference between the groups.

Conclusion: In advanced HCC with major vascular involvement, patients who had RR with PA of greater 78% achieved a similar survival to those who had CR. The surgeon should still proceed with RR in those patients with serum PA of >78% if CR does not seem feasible on preoperative evaluation.

Hepatocellular carcinoma (HCC) is one of the world's most common malignancies, especially in East-Asian countries. The prognosis of advanced HCC remains poor, particularly in patients with tumor thrombi (TT) in major branches of the portal vein (PV) and inferior vena cava (IVC).[1–13] Hepatic resection has been accepted as the only means of cure for patients with HCC.[14–27] However, the number of surgical candidates is

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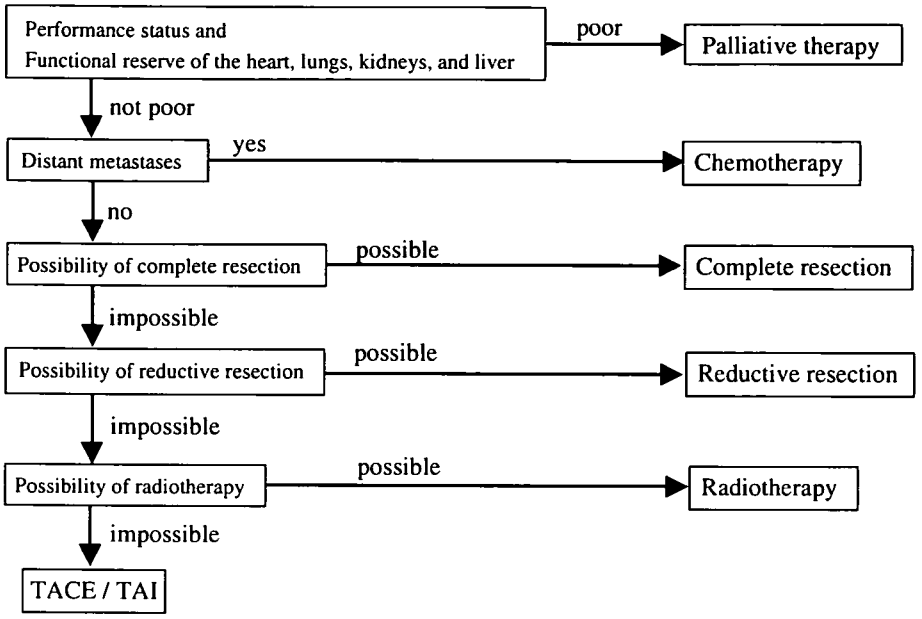

Figure 1. Strategy of treatment for advanced hepatocellular carcinoma (HCC) with major vascular involvement.

limited because of advanced HCC and/or poor hepatic reserve function of the liver as a whole at the time of diagnosis. In many cases ,it is not possible to perform curative resection because of multiple intrahepatic metastases, vascular involvement, and/or distant metastases. Almost all patients with unresectable tumors die within several months.[28–31] To overcome these poor results, several attempts have been made to perform reduction surgery with subsequent multidisciplinary treatment.[32–37] However, there has been little investigation on the indications for reduction surgery for patients with advanced HCC.

The aim of this study was therefore to clarify the indications for reduction surgery in patients with advanced HCC with TT and to identify patient groups that might benefit from it.

PATIENTS AND METHODS

From July 1992 to October 2004, 161 patients with a diagnosis of advanced HCC with major vascular involvement were seen consecutively at the National Cancer Center Hospital East. We analyzed the prognostic factors and survival rates of these patients retrospectively. Briefly, advanced HCC with major vascular involvement is defined by the presence of TT in the first branches of the PV, the main PV, or the IVC via the hepatic vein (HV). Diagnosis of HCC, presence of tumor thrombi, and the presence of distant metastases were based on the images of ultrasonography, dynamic computed tomography (CT), magnetic resonance imaging, and angiography. Various organ function was assessed by chest X-ray, serum biochemical examination, spirometry, and electrocardiography.

Our treatment strategy for advanced HCC with major vascular involvement is shown in Fig. 1. First, performance status and functional reserve of the heart, lungs, kidneys, and liver were evaluated, and patients with a poor condition were treated with palliative therapy (PT). Patients with distant (extrahepatic) metastases were treated with systemic chemotherapy (CT) if their condition was satisfactory. Patients with a good condition and no distant metastases were considered for complete resection (CR). Hepatectomy was indicated according to criteria based on tumor extension and hepatic functional reserve.[1,2] If CR could not be performed, the possibility of reductive resection (RR) was considered. RR is defined in our institute as resection of the main tumor or the main tumor plus satellite tumors around the main tumor, with satellite tumors in the remnant liver classified as unresectable. In cases with TT in the PV or HV, TT are removed with the liver lobe containing the main tumor. If these surgical approaches are not possible, in the next phase, it is considered whether radiotherapy (RT) will be tolerated or not. Radiotherapy is indicated if there are gastroduodenal or small intestine inside the radiation field. Finally, if RT is indicated, patients are treated with transcatheter arterial chemoembolization (TACE) or transcatheter arterial infusion chemotherapy (TAI). TACE is performed by infusion of a mixture of lipiodol (5 ml) and farmorubicine (50 mg), followed by gelfoam embolization. If liver function becpmes poor and portal vein flow is poor with tumor thrombi,

Table 1.
Patient profile

	Complete resection	Reductive resection	Radiotherapy	TACE/TAI	Chemotherapy	Palliative therapy
No. of patients (%)	16 (10)	16 (10)	18 (11)	73 (45)	8 (5)	30 (19)
Age (years)	57 ± 2.0	53 ± 2.8	59 ± 2.6	61 ± 0.9	62 ± 3.1	62 ± 1.7
Gender (M/F)	14/2	14/2	16/2	58/15	8/0	27/3
Virus type: B / C / non B non C	7/5/5	8/5/4	4/12/3	28/42/11	3/5/2	10/24/1
Aspartate aminotransferase (IU/dl)	54 ± 4	100 ± 21	89 ± 15	125 ± 15	73 ± 15	239 ± 90
Total bilirubin (mg/dl)	0.9 ± 0.04	0.8 ± 0.06	1.1 ± 0.2	1.3 ± 0.1	1.3 ± 0.3	4.8 ± 1.3
Albumin (g/dl)	3.9 ± 0.1	3.5 ± 0.1	3.3 ± 0.1	3.5 ± 0.1	3.6 ± 0.2	3.1 ± 0.1
ICG R15 (%)	14 ± 2.2	15 ± 1.7	27 ± 3.5	29 ± 1.9	12 ± 4.9	35 ± 4.3
Prothrombin activity (%)	79 ± 3.7	77 ± 3.3	71 ± 45	83 ± 10	68 ± 5.1	66 ± 3.6
Platelet ($\times 10^4/\mu l$)	19 ± 1.8	20 ± 1.9	16 ± 2.3	15 ± 1.0	14 ± 2.6	14 ± 1.3
AFP (pg/ml)	43 ± 27	83 ± 62	5.1 ± 1.9	62 ± 21	93 ± 93	82 ± 38
Child-Pugh score						
A	13	12	4	32	3	4
B	3	4	10	32	4	13
C	0	0	4	9	1	13

TACE / TAI: transcatheter arterial chemoembolization/transcatheter arterial infusion chemotherapy; ICG R15: Indocyanine green retention value at 15 minutes; AFP: α-fetoprotein.
Values represent (mean ± SE).

only TAI with farmorubicine is performed. After treatments with RR and RT, TACE/TAI are combined, repeated until the remnant tumor completely disappears on computed tomography angiography (CTA). management with respect to detection and staging of HCC is discussed with hepatobiliary-pancreatic surgeons, physicians, and diagnostic radiologists, and determined.

Statistical analysis was performed by the chi-square test and Mann–Whitney *U*-test. Survival rates were calculated using the Kaplan Meier method. Survival curves were compared using log-rank test. The Cox proportional hazard model was used to assess clinical factors influencing survival benefit in the RR group. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Tables 1 and 2 show patient characteristics in the main treatment groups. Among the 161 advanced HCC patients, 32 (20%) underwent surgical resection (16 CR, 16: RR). Eighteen patients (11%) received RT, 73 (45%) underwent TACE or TAI, 8 (5%) with distant metastases received systemic chemotherapy (CT), and 30 (19%) received palliative therapy (PT). Morbidity and mortality of 32 patients with surgical treatments (CR and RR) are demonstrated in Table 3. There was no statistical difference between the CR group and the RR group in the postoperative hospital stay. Table 4 and Fig. 2 show the median, 3-month, 1-year, and 5-year survival rates in each treatment group. There were 5-year survivors in the CR group only and the survival rate was 37%. Excluding the CR group, patients in the RR group had a higher 1-year survival rate than the other treatment groups. However, there was no significant difference in overall survival rates of the RR, RT, and TACE/TAI groups. Table 5 shows the results of univariate analysis used to identify significant preoperative factors for overall survival in patients treated with RR. Among the 13 preoperative factors, 4 significant factors were identified by univariate analysis: age, aspartate aminotransferase (AST), prothrombin activity (PA), and tumor size. Table 6 shows the results of multivariate analysis using Cox's proportional hazards model. Multivariate analysis was performed on the 4 preoperative factors (age, AST, PA, and tumor size) for overall survival that reached statistical significance in univariate analysis ($P < 0.05$), as shown in Table 5. Among them, serum PA was identified as a significant independent preoperative factor for overall survival. The distribution of serum PA for each patient treated with RR is shown in Fig. 3. The value of serum PA that gave the maximum sensitivity and specificity for the survival period was 78%. Figure 4 shows a comparison of overall survival rates after RR between serum PA of >78% and PA of ≤78%. Survival rate in patients with PA of ≤ 78% was significantly lower than that of patients with PA of >78% ($P = 0.0004$). Median survival time of patients with serum

Table 2.
Tumor factors of 161 patients with advanced hepatocellular carcinoma (HCC)

	Complete resection	Reductive resection	Radiotherapy	TACE/TAI	Chemotherapy	Palliative therapy
No. of patients (%)	16 (10)	16 (10)	18 (11)	73 (45)	8 (5)	30 (19)
Tumor size (cm)						
<5	1 (6)	0	3 (17)	11 (15)	2 (25)	2 (7)
5–10	7 (44)	6 (38)	9 (50)	42 (58)	2 (25)	19 (63)
>10	8 (50)	10 (63)	6 (33)	20 (27)	4 (50)	9 (30)
No. of tumor nodules						
1	9 (56)	0	8 (44)	12 (16)	4 (50)	4 (13)
2–5	3 (19)	5 (31)	1 (6)	8 (11)	3 (38)	2 (7)
>5	4 (25)	11 (69)	9 (50)	53 (72)	1 (13)	24 (80)
Bilobar tumors	2 (13)	14 (88)	13 (72)	54 (74)	5 (63)	27 (90)
Presence of major PVT	13 (81)	14 (88)	18 (100)	69 (95)	7 (88)	29 (97)
Presence of major HVT	8 (50)	4 (25)	2 (11)	15 (21)	3 (38)	9 (30)

TACE/TAI: transcatheter arterial chemoembolization/transcatheter arterial infusion chemotherapy; PVT: portal vein thrombosis; HVT: hepatic vein thrombosis.

Table 3.
Morbidity and mortality of 32 patients with surgical treatment

	Complete resection	Reductive resection	*P* value*
No. of patients	16	16	
Morbidity	10/16	13/16	NS
Wound infection	4	6	
Pleural effusion	3	2	
Ascites	2	0	
Bile leakage	4	7	
Mortality	1/16[a]	1/16[b]	NS
Postoperative hospital stay (days) (mean)	27	27	NS

NS: nonsignificant values.
[a]Death due to liver failure on postoperative 15th day.
[b]Death due to massive bleeding intraoperatively.
*Statistical significance between both groups was analyzed by chi-square test and Mann–Whitney *U*-test.

Table 4.
Survival rate of 161 patients with advanced hepatocellular carcinoma (HCC) in each treatment group

			Survivors (%)		
Treatment	Number	Median survival (months)	3-month survival	1-year survival	5-year survival
Complete resection	16	9.1	93	74	37
Reductive resection	16	6.2	93	39	0
Radiotherapy	18	6.6	72	28	0
TACE/TAI	73	3.8	67	25	0
Chemotherapy	8	3.0	50	0	0
Palliative therapy	30	0.9	10	0	0

TACE/TAI: transcatheter arterial chemoembolization/transcatheter arterial infusion chemotherapy.

PA of >78% who underwent RR was 13.9 months, and that of patients who underwent CR was 9.1 months, with no survival difference between CR patients and RR patients with PA of greater 78% (Fig. 5). Median survival time of patients with serum PA of ≤78% who underwent RR was 4.9 months, that of patients who received RT was 6.6 months, and that of patients received TACE/TAI was 3.8 months, with no survival difference among RT patients, TACE/TAI patients, and RR patients with PA less than 78% (Fig. 5).

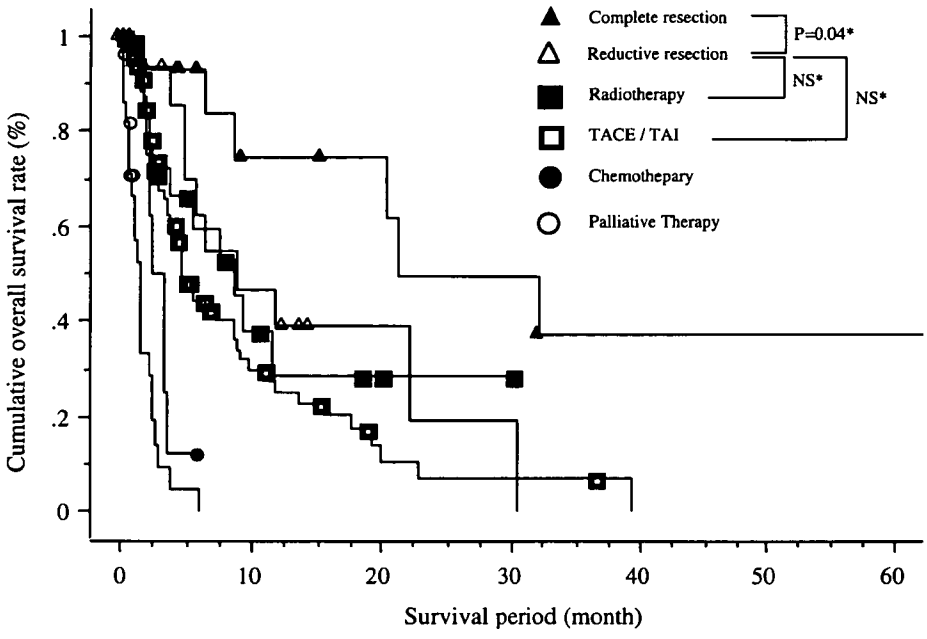

Figure 2. Cumulative survival curves obtained by the Kaplan–Meier method for each treatment (statistical significance between groups was analyzed by log-rank test).

Table 5.
Clinical factors influencing cumulative survival rate of patients in reductive resection group analyzed by univariate analysis

Clinical factors	*P* value
Age	0.0148*
Gender	0.8293
Aspartate aminotransferase	0.0136*
Total bilirubin	0.1719
Albumin	0.6645
ICG R15	0.0580
Prothrombin activity	0.0092*
Platelet	0.8851
AFP	0.5337
Tumor size	0.0072*
No. of tumor nodules	0.1192
Presence of major PVT	0.9641
Presence of major HVT	0.6589

ICG R15: Indocyanine green retention value at 15 minutes; PVT: portal vein thrombosis; HVT: hepatic vein thrombosis; AFP: α-fetoprotein.
*Statistically significant.

Table 6.
Clinical factors influencing cumulative survival rate of patients in reductive resection group analyzed by multivariate analysis

Clinical factors	*P* value
Age	0.5691
Aspartate aminotransferase	0.0894
Prothrombin activity	0.0203*
Tumor size	0.0927

*Statistically significant.

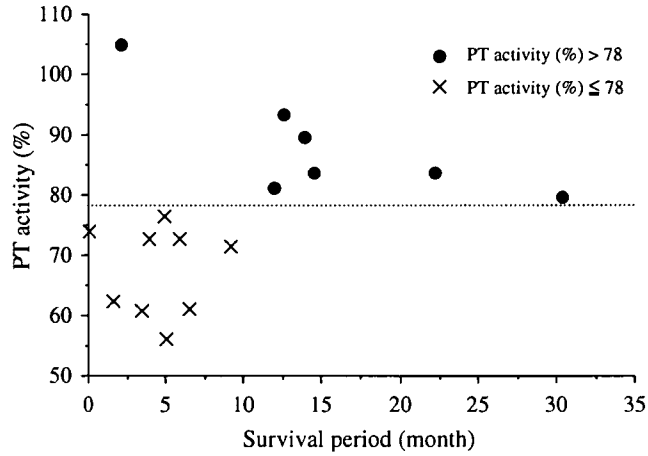

Figure 3. Patient distribution for each prothrombin (PT) activity in reductive resection group.

DISCUSSION

Development of TT in the first branch of the PV, the main PV, or the IVC via the HV is a feature of advanced HCC. The prognosis for such patients is extremely poor, and survival is generally limited to a few months after diagnosis.[3–15,19] Cases of advanced HCC with TT are usually not controllable by alternative therapies such as TACE/TAI, CT, and RT. As shown in Fig. 2, only patients who underwent CR of tumors with direct removal of TT had long-term survival. Our results demonstrated no significant difference between the RR group and other treatment groups (RT and TACE/TAI). However, if advanced HCC patients with TT cannot receive CR, RR with

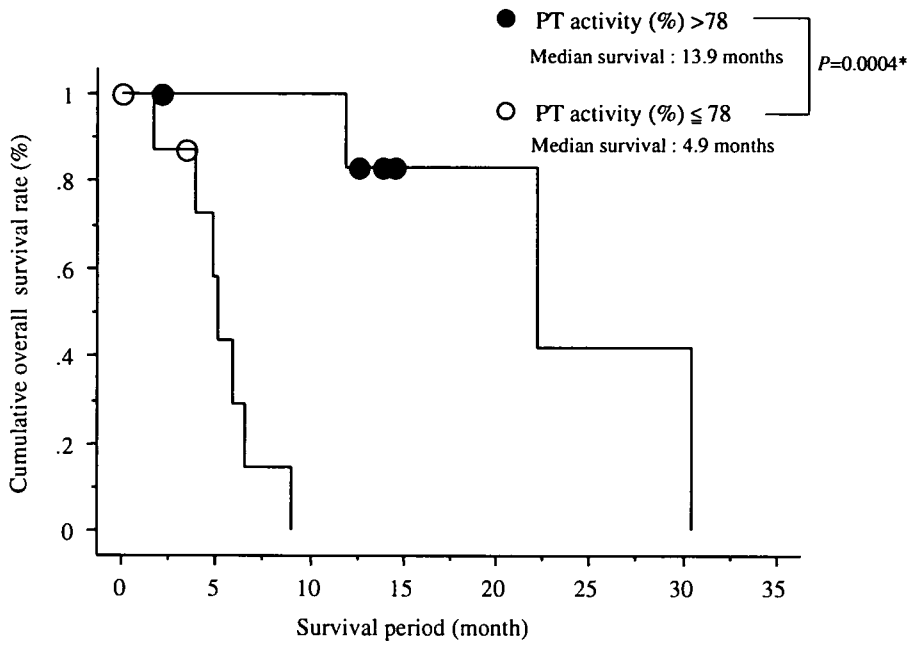

Figure 4. Cumulative survival curves obtained by the Kaplan-Meier method for each prothrombin (PT) activity in reductive resection group (statistical significance between groups was analyzed by log-rank test).

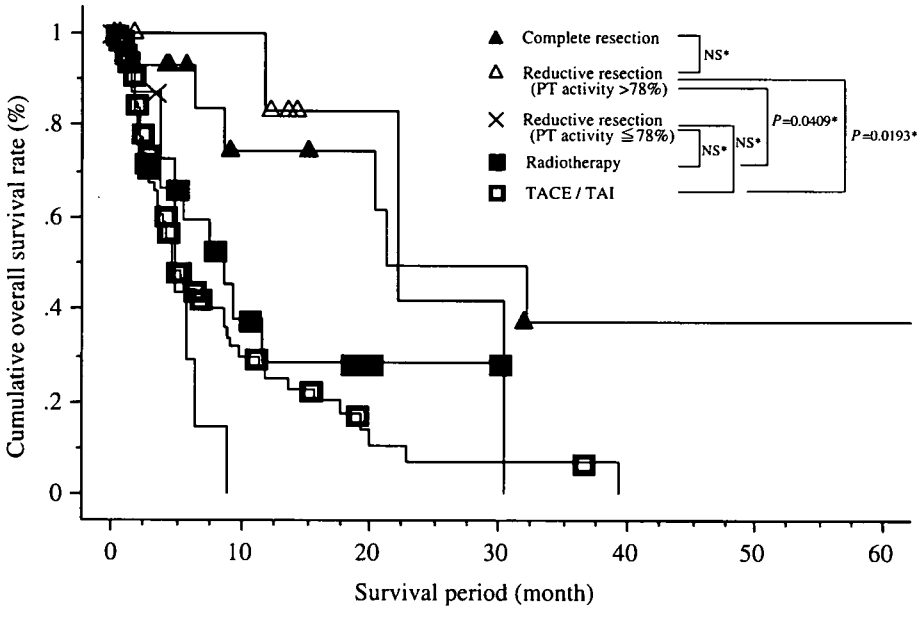

Figure 5. Comparison of cumulative survival curves obtained by the Kaplan–Meier method for each treatment group (statistical significance between groups was analyzed by log-rank test).

direct removal of TT might be the only treatment that offers hope of prolonged survival. We consider that RR holds the promise of prolonged survival in advanced HCC patients. There are several reports concerning the efficacy of RR for patients with advanced HCC.[15,19,34,35,37,38] Moreover, there are some reports that hepatectomy for large HCC (tumors greater than 10 cm) is a safe procedure when performed in high-volume centers.[22,36,39–42] We have also demonstrated that postoperative hospital stay in the RR for multiple large HCC was similar to the CR group and that RR could be performed safely. Although morbidity was high and one patient died within 30 days after operation in our surgical treatment groups (CR and RR groups: CR patient died in 1996 and RR patient died in 1995), morbidity was much lower recently because surgical technique and perioperative management were improving.

When we judged that the liver function would tolerate resection of the main tumor and direct removal of TT even if intrahepatic metastases remained in the remnant liver, we performed RR. In the present study, we evaluated the efficacy of RR for advanced HCC with major

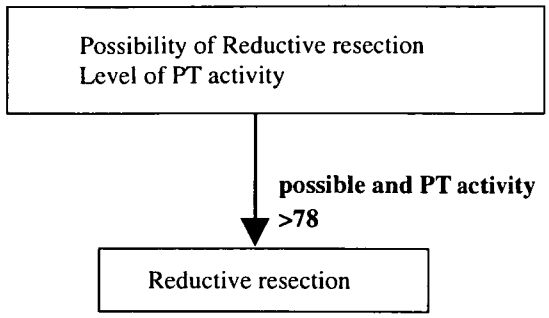

Figure 6. New indication of reductive resection for advanced hepatocellular carcinoma (HCC) with major vascular involvement.

vascular involvement. Yamamoto *et al.*[34] suggested remnant tumor index (RTI) as a significant prognostic factor in advanced HCC patients who underwent RR. RTI was calculated on the basis of the size and number of residual HCC nodules after RR. However, Asahara *et al.*[43] reported that long-term survivors did not always meet the criteria for RTI and that the indication for RR in HCC patients with multiple intrahepatic metastases was relatively small primary tumors that could be removed by single segmentectomy. These reports about the efficacy of RR included cases of advanced HCC without TT. In our study, we evaluated the characteristics of advanced HCC with major vascular involvement; primary tumors were larger than 5 cm in diameter, and the number of HCC nodules was greater than 5 in many cases. Our indication for RR for advanced HCC with TT in major vessels (first branch of the PV, the main PV, or the IVC) was serum PA of >78% (Fig. 6). Prolongation of survival in advanced HCC patients with serum PA of >78% can be expected with RR with direct removal of TT. The survival of these patients under our new indication for RR was similar to the survival of advanced HCC patients who underwent CR. On the other hand, the survival of advanced HCC patients with serum PA of ≤78% was similar to that of patients who received RT or TACE/TAI; therefore, it is not recommenced that patients with serum PA of ≤78% undergo RR with direct removal of TT. Unnecessary surgical stress can be avoided in patients who cannot be expected to achieve prolonged survival by RR.

In conclusion, if complete resection does not seem feasible for patients with advanced HCC with major vascular involvement on preoperative evaluation, the surgeon should still proceed with debulking surgery in those patients with serum PA of >78% because a reductive resection portends to survival benefit even if there is not complete clearance.

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Original Paper

The Role of a Protease Inhibitor against Hepatectomy

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ABSTRACT

Background/Aims: Nafamostat Mesilate (NM) is a synthetic serine protease inhibitor that is capable of inhibiting the various coagulation factors. To determine whether NM may also be useful in attenuating operative invasiveness, we investigated the effects of perioperative administration of NM on postoperative serum levels of proinflammatory cytokine IL-6 and hepatocyte growth factor (HGF).

Methodology: Thirty patients undergoing hepatectomy with hepatocellular carcinoma, biliary carcinoma and metastatic colorectal cancer were enrolled in this study. These patients were separated into two groups; high invasive group (resected liver volume: 1000cm^3 <) and less invasive group (resected liver volume: 1000cm^3 >). The high invasive group of 11 patients received perioperative administration of NM (Group NM), while the less invasive group of 19 patients did not (Group C). Serum levels of IL-6, HGF and soluble IL-6 receptor (sIL-6R) were simultaneously measured on preoperative and postoperative day ('day 0', 'day 7').

Results: Serum IL-6 levels on day 0 were significantly elevated and returned to preoperative levels on day 7 in both groups, and the serum IL-6 level in Group NM on day 0 was significantly lower than that in Group C on day 0. Serum HGF levels on day 0 and day 7 were significantly higher in Group NM than those in Group C. Compared with healthy control subjects, the higher serum level of HGF on the preoperative day in all patients was attributable to tumor-burden. The sIL-6R levels on day 0 decreased in both groups, and their levels in Group NM were significantly lower than those in Group C, suggesting that increased synthesis of IL-6/sIL-6R complex which could accelerate liver regeneration.

Conclusions: These results suggested that perioperative administration of NM may attenuate surgical stress by decreasing production of proinflammatory cytokine IL-6, and may accelerate liver regeneration through stimulation with the IL-6/sIL-6R complex and possible involvement of increased production of HGF.

KEY WORDS: Protease inhibitor; Nafamostat mesilate; Hepatectomy; Interleukin-6; soluble Interleukin-6 receptor; Hepatocyte growth factor

ABBREVIATIONS: Nafamostat Mesilate (NM); Hepatocyte Growth Factor (HGF); Soluble Interleukin-6 Receptor (sIL-6R); Hepatocellular Carcinoma (HCC); C-Reactive Protein (CRP)

INTRODUCTION

Nafamostat mesilate (6-amino-2-naphthyl p-guanidinobenzoate dimethansuifonate, NM) is a synthetic protease inhibitor generated during the coagulation cascade as well as in the inflammatory process (1,2). NM inhibits coagulation factors such as factor VIIa and thrombin (3), and has been found to be effective in treating animals with induced sepsis (4,5). Moreover, regarding its anticoagulant effects, recent reports demonstrated that NM had inhibitory effects on the production of polymorphonuclear leukocyte elastase and Interleukin-6 (IL-6) and IL-8 in human monocytes (6,7).

In liver, IL-6 is secreted by non-parenchymal cells such as Kupffer cells. Secreted IL-6 acts on neighboring hepatocytes to stimulate liver regeneration and repair (8). It also acts on cells by binding the soluble IL-6 receptor (sIL-6R), either in its membrane-bound or soluble form. And this IL-6/sIL-6R complex binds and induces liver regeneration and hepatoprotection (9).

To determine whether NM may also be useful in attenuating surgical stress and has a hepatoprotective effect or stimulates liver regeneration, we investigated the effects of perioperative administration of NM on postoperative serum levels of proinflammatory cytokine against hepatectomy.

METHODOLOGY

Thirty consecutive patients undergoing hepatectomy with hepatocellular carcinoma (HCC), biliary tract carcinoma and metastatic colorectal cancer were enrolled in this study.

All liver resections were performed under conditions of continuous hepatic pedicle occlusion. Hepatic parenchymal transection was performed with clamp crushing methods. Liver resections were included in 9 major hepatectomies (2 ≤ segment), 11 minor hepatectomies (1 ≥ segment) and 10 partial resections.

Hepato-Gastroenterology 2006; 53:115-119

These patients were separated into two groups; high invasive group (resected liver volume: 1000cm^3<) and less invasive group (resected liver volume: 1000cm^3>). The high invasive group of 11 patients received perioperative administration of NM (Group NM), while the less invasive group of 19 patients did not (Group C). In group NM, NM was continuously administered at a dosage of 0.1mg/kg/hr through a peripheral vein starting 30 minutes before the operation for 24 hours.

Eleven patients in group NM included 6 with HCC, 1 with biliary tract carcinoma and 4 with metastatic colorectal carcinoma. Nineteen patients in group C included 13 with HCC, 3 with biliary tract carcinoma and 3 with metastatic colorectal carcinoma **(Table 1)**. There were no significant differences in age and gender between groups.

TABLE 1 Patient Profile

	Group C	Group NM	*P*
No. of patients	19	11	
Age (years)	68±1.8	68±2.5	*NS
Sex (M/F)	15/4	7/4	§NS
Viral Hepatitis	10	5	§NS
	(Type B: 1, Type C: 9)	(Type B: 4, Type C: 1)	§NS
Disease			
Hepatocellular carcinoma	13	6	
Biliary tract carcinoma	3	1	
Liver metastases of colorectal carcinoma	3	4	
Liver Resection			§*P*=0.0021
Partial Resection	10	0	
Minor 1 ≥ Segment	7	4	
Major 2 ≤ Segment	2	7	

NM: Nafamostat Mesilate.
Values represent (mean ± SE. NS: Not significant); *Statistical significance between groups was analyzed by Mann-Whitney's U test. §Statistical significance between groups was analyzed by Chi-square test.

TABLE 2 General Comparison of Patients in Preoperative, Surgical and Postoperative States

	Group C	Group NM	*P*
Preoperative liver function			
Alanine aminotransferase (ALT) (IU/dL)	68±16	50±10	*NS
Total bilirubin (T-Bil) (mg/dL)	0.9±0.1	1.0±0.1	*NS
Albumin (Alb) (g/dL)	3.7±0.1	3.8±0.1	*NS
Prothrombin time (PT) (%)	12±0.1	12±0.2	*NS
$ICGR_{15}$ (%)	15±2.3	13±1.6	*NS
Platelet (x10^4/μL)	17±2.2	21±1.4	*NS
C-reactive protein (mg/dL)	0.2±0.1	0.3±0.1	*NS
Surgical stress			
Operative time (min)	200±32	370±49	*0.0055
Hepatic ischemic time (min)	52±6.0	98±15	*0.0034
Blood loss (mL)	880±190	3500±1300	*0.0133
Resected liver weight (g)	110±30	430±68	*0.0002
Resected liver volume (cm^3)	250±59	1400±83	*<0.0001
Postoperative liver function (day 7)			
Alanine aminotransferase (ALT) (IU/dL)	71±7.9	91±17	*NS
Total bilirubin (T-Bil) (mg/dL)	1.3±0.4	1.3±0.3	*NS
Albumin (Alb) (g/dL)	3.4±0.1	3.3±0.1	*NS
Prothrombin time (PT) (%)	12±0.1	12±0.2	*NS
Platelet (x10^4/μL)	20±2.0	21±2.2	*NS
C-reactive protein (mg/dL)	3.2±0.6	7.4±1.5	*0.0059

Values represent (mean ± SE. NS: Not significant), *Statistical significance between groups was analyzed by Mann-Whitney's U test.

In all patients peripheral blood samples were collected before operation ('preop'), immediately after operation ('day 0'), and on day 7 after operation ('day 7'). Plasma concentrations of IL-6 (Fujirebio Inc., Tokyo, Japan), sIL-6R (R&D systems, Minneapolis, MN), hepatocyte growth factor (HGF, Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) were simultaneously measured on preoperative and postoperative day ('day 0' and 'day 7') using an enzyme-linked immunosorbent assay (ELIZA) kit. Moreover, the preoperative serum levels of HGF in all patients were compared with 109 healthy control subjects.

Percent recovery of liver size was calculated with resected liver mass and volumetric analysis by computed tomography of preoperative and postoperative (4 wk after hepatectomy) liver mass. A: [surgically resected liver volume] was considered as 'an expected liver mass of full recovery', and B: [resected liver mass - (preoperatively measured liver mass - postoperatively measured liver mass)] was considered as 'a real recovery of liver'. B divided by A provides recovery ratio of liver, which was expressed as percent recovery of liver.

Statistical Analysis

All data were expressed as means ± SE. The Mann-Whitney's U test and the Chi-square test were used to analyze samples, respectively. *P* values less than 0.05 were considered statistically significant.

RESULTS

General Comparison of Patients in Preoperative Liver Function, Surgical Stresses, Postoperative Liver Function and Liver Recovery Ratio

There was no significant difference between group C and group NM in preoperative liver function. All factors of surgical stress in group NM were significantly higher than those in group C **(Table 2)**. The postoperative rise of C-reactive protein (CRP) and postoperative morbidity in group C was significantly lower than those in group NM. No significant differences were observed between the two groups in postoperative other liver function, mortality and hospitalization **(Tables 2 and 3)**. In liver recovery ratio, there was no significant difference between both groups **(Figure 1)**.

Comparison of Serum Levels IL-6 and sIL-6R between Group C and Group NM

Serum IL-6 levels on day 0 were significantly elevated and returned to preoperative levels on day 7 in both groups, and the serum IL-6 level in group NM on day 0 was significantly lower than that in group C on day 0. The sIL-6R levels on day 0 decreased in both groups, and their levels in group NM were significantly lower than those in group C **(Table 4)**.

Serum Level HGF in All Patients with Each Disease

In preoperative serum level of HGF, there was a significant difference between all patients enrolled in this study and healthy control subjects. All serum HGF levels on preop, day 0 and day 7 in group NM were higher than those in group C **(Table 5)**.

DISCUSSION

A synthetic protease inhibitor has an inhibitory effect on various serine proteases such as trypsin, thrombin, activated factor X, kallikrein, neutrophil elastase, and activated complement components (1). Effects of synthetic protease inhibitors on microcirculatory and coagulation disorder and on organ failure such as septic ARDS have also been reported (10-14).

Recently, preoperative administration of protease inhibitor substantially ameliorated hepatocyte injury induced by ischemia and reperfusion in human patients when liver resection was performed under continuous inflow occlusion (15). Moreover, there were some reports that serine protease inhibitors may play an important role in liver regeneration (16,17).

These many studies using animal models have demonstrated that hepatically-derived cytokines are produced in the process of hepatic ischemia and reperfusion (18-21). IL-6 is a proinflammatory cytokine that mediates the acute-phase inflammatory response to tissue injury. The greater the surgical stresses, the higher the elevation of serum IL-6 (22-24). Although the precise role of IL-6 in hepatocyte injury remains to be clarified, at least excess production of IL-6 may be associated with adverse events after liver resection in humans because there were many reports that the over-production of plasma IL-6 is followed by major postoperative elevation of plasma transaminase activities after prolonged hepatic inflow occlusion (25-27). However, recent reports have demonstrated that HGF and IL-6 could promote hepatic survival by stimulating liver regeneration and providing hepatoprotection in a variety of liver injury models, including Fas-mediated injury, toxic damage caused by hepatotoxins (such as tetrachlorcarbonide), and ischemic liver injury (28-32). Particularly, IL-6 is a critical proregenerative factor and acute-phase inducer in the liver that also confers resistance to liver injury by hepatic toxins, ischemia, and Fas. Its effects are mediated almost exclusively on hepatocytes within the liver (33). Secreted IL-6 acts on neighboring hepatocytes in a paracrine fashion to stimulate liver regeneration and repair (8). IL-6 bound to the sIL-6R signals via gp130 and Janus kinase-1 (JAK-1), leading to activation of the Stat3 transcription factor and the MAPK signal transduction cascade (33,34). In this way, the IL-6 signal transduction pathway in liver injury and regeneration was clarified. Our results would also suggest that increased synthesis of IL-6/sIL-6R complex which could accelerate liver regeneration.

HGF could be produced in many organs or released from the extracellular matrix of the liver. HGF is a potent stimulator of DNA synthesis in hepatocytes and interacts with other growth factors. After partial hepatectomy, the increased tyrosine phosphorylation of c-MET/HGF-receptor is seen in the hepatocytes. The HGF/c-MET system is also involved in liver regeneration. There is increased synthesis of HGF by nonparenchymal cells after partial hepatectomy (35,36), and therefore, increased HGF production is expected on liver injury and has been described as stimulating liver regeneration factor. And its supportive roles in liver regeneration are expected in many clinical situations.

In the other hand, HGF may well be an important factor in tumor propagation and development of distant metastases because of its profound impact on cell proliferation and motility (37). And then, it has already been reported that HGF has been a useful

TABLE 3 General Comparison of Patients in Postoperative Outcomes

	Group C	Group NM	*P*
Postoperative mortality	1/19	0/11	§NS
Postoperative morbidity	1/19	4/11	§0.0288
Wound infection	1	1	
Pulmonary infarction	0	1	
Bile leakage	0	1	
Paralytic ileus	0	1	
Postoperative hospitalization (days)	15±3.9	20±4.6	§NS

Values represent (mean ± SE. NS: Not significant), *Statistical significance between groups was analyzed by Mann-Whitney's U test. §Statistical significance between groups was analyzed by Chi-square test.

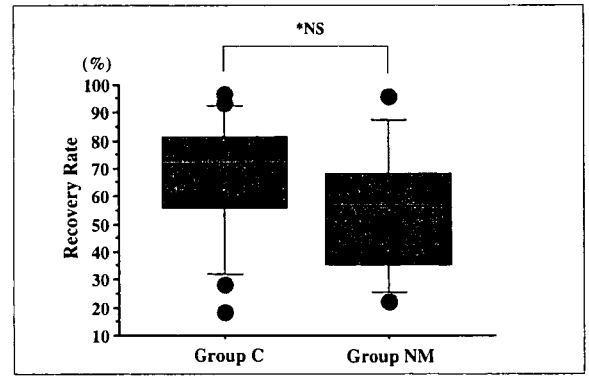

FIGURE 1 Percent recovery of liver size 4 weeks after hepatectomy. Percent recovery of liver size was calculated by volumetric analysis by resected liver volume, computed tomography of liver preoperatively and 4 wk after hepatectomy. *Statistical significance between groups was analyzed by Mann-Whitney's U test.

TABLE 4 Comparison of Serum Levels of IL-6, sIL-6R, HGF With/Without Nafamostat Mesilate

		Group C	Group NM	*P*
IL-6 (pg/mL)	Preop	4.3±1.2	3.0±0.7	NS
	Postop (day 0)	240±170	180±51	0.0454
	Postop (day 7)	23±6.1	49±15	NS
sIL-6R (pg/mL)	Preop	29000±2000	24000±1700	NS
	Postop (day 0)	26000±1500	17000±850	0.0007
	Postop (day 7)	28000±1800	24000±2100	NS

Values represent mean ± SE. Statistical significance between groups was analyzed by Mann-Whitney's U test.

TABLE 5 Comparison of Serum Level of HGF in Preoperative Patients and Normal Control, Comparison of Serum Levels of HGF With/Without Nafamostat Mesilate in Postoperative Patients

HGF (pg/mL)	All patients (n=30)	Normal control (n=109)	*P*
Preop	445±61	293±5.2	0.0002
	Group C	**Group NM**	***P***
Postop (day 0)	500±80	900±390	NS
Postop (day 7)	460±44	640±80	0.0210

Values represent mean ± SE. Statistical significance between all patients and normal control was analyzed by Mann-Whitney's U test.

indicator for predicting the status of HCC, colorectal cancer and cholangiocellular carcinoma (36,38-42). Compared with group C, our results demonstrated that the serum level of HGF was higher in group NM. However, the preoperative serum level of HGF was high in group NM, and we wondered whether that result was reflected by the activity of cancer cell. We evaluated the difference between the serum levels of HGF in cancer patients and healthy control subjects. We found a significant difference between patients enrolled in this study and healthy control subjects, which was consistent with a previous report that the serum HGF concentration of patients with colorectal cancer was significantly higher than that in healthy normal control level of 174±14pg/mL as means ± SE (40). The HGF level in the healthy control in our study of 293±5.2pg/mL was higher than that in a previous report (40), which was attributable to ELISA kits used.

Excluding the role of the serum HGF concentration as predicting index of tumor propagation, we considered that the effect to liver regenerative rate was reflected by the serum levels of HGF on day 0 and day 7. In the serum levels of HGF on day 0 and day 7, the level of HGF in group NM was higher than that in group C, we considered that these levels of HGF were increased because the synthesis of HGF was stimulated by the administration of NM. Shimomura *et al.* (43) also reported that blood-coagulation factor XIIa and HGF activator activated HGF, and the HGF-converting activity of the HGF activator was not prevented by the serine protease inhibitors. Though there were some reports that liver regeneration was influenced by the loss of liver volume by liver resection (44,45), these results might insinuate that the higher level of HGF, the better the liver regeneration. And then, protease inhibitor may have a good role in the liver regeneration.

The present study demonstrated that although no significant difference was observed between both groups in the liver regenerative rate, this result seemed to be affected by the high incidence of postoperative morbidity in group NM. Indeed, the postoperative CRP level was significantly higher in group NM in the present research. Weiss *et al.* (46) reported that the growth rate of hepatic regeneration was lower in fulminant sepsis than in mild sepsis. The postoperative morbidity is very susceptible to surgical stresses, all indicators of the surgical stress were higher in group NM than in group C. Despite the high incidence of postoperative morbidity and high surgical stresses in group NM, postoperative recovery rate of liver in group NM was equivalent to that of liver in group C. These results suggested that the perioperative administration of NM may attenuate surgical stress by decreasing production of proinflammatory cytokine IL-6, and may accelerate liver regeneration through increased production of HGF and stimulation with the IL-6/sIL-6R complex. It would be possible that much better liver regeneration is induced by the administration of NM if we could improve our surgical techniques and keep the lower incidence of postoperative morbidity in the liver surgery.

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Selection Criteria for Reduction Hepatectomy in Multiple Advanced Hepatocellular Carcinoma

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Abstract. *Background: Few studies have compared the prognostic impact of reduction hepatectomy (RH) for advanced hepatocellular carcinoma (HCC) with that of non-surgical treatment or curative hepatectomy. Patients and Methods: The treatment outcome of 30 RH patients was compared to that of two control groups: control group A, including 71 patients who underwent curative hepatectomy; control group B, including 106 patients who did not receive definitive local therapy or best supportive care. Results: In patients with tumor extension in >50% of the liver, 1-year survival rates for patients according to treatment (RH, control A and B) were 50%, 90% and 11% and 3-year survival rates were 42%, 60% and 0%, respectively. There was no significant difference between RH and control A, but there was a significant difference between RH and control B. Conclusion: RH could be recommended to patients with multiple advanced HCC extending to >50% of the whole liver.*

Hepatic resection is the only treatment that offers a hope of cure with long-term survival in patients with HCC. However, the indications for radical hepatectomy for hepatocellular carcinoma (HCC) remain limited for patients with multiple intrahepatic metastases (1). If hepatectomy with curative intent for multiple advanced HCCs cannot be performed, the possibility of volume reduction hepatectomy (RH) for those HCCs is often considered, with the aim of decreasing target tumor cells so that effective post-operative treatment can be carried out. The efficacy of RH for advanced HCC has been reported by several studies (2-5), and we have also performed RH for multiple advanced HCC.

The aim of this study was to evaluate the long-term results of RH for patients with multiple HCC, and to validate the indications for RH compared to other treatments and optimize patient selection.

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Key Words: Reduction hepatectomy, advanced hepatocellular carcinoma, selection criteria.

Patients and Methods

From July 1992 to May 2005, 1,001 patients with a diagnosis of HCC with no distant (extrahepatic) metastases were examined consecutively at the National Cancer Center Hospital East, Japan. Of these HCC patients, 30 underwent RH. Their treatment outcome was compared retrospectively with that of two control groups selected among the remaining 971 patients with a similar background to the RH patients. The selection criteria (background factors) were: total bilirubin <2.4 mg/dl, albumin >2.7 g/dl, no ascites, Child-Pugh score <9 points, multiple tumors, main tumor >44 mm in diameter, Okuda stage I or II (6), and BCLC (Barcelona Clinic Liver Cancer) stage B or C (7). Control A included 71 patients who underwent hepatectomy with curative intent. Control B included 106 patients who did not receive definitive local therapy (hepatectomy, percutaneous ablation therapy or proton beam radiotherapy) or best supportive care.

The indications for hepatectomy were determined according to criteria based on tumor extension and hepatic functional reserve (8, 9). As our treatment strategy for advanced HCC, whether or not hepatectomy with curative intent could be performed was considered first. When hepatectomy with curative intent could not be performed, the possibility of RH was considered. RH was defined at our institute as resection of the main tumor or main tumor plus satellite tumors around the main tumor, with satellite tumors in the remnant liver classified as unresectable. If this surgical treatment for advanced HCC was not feasible, radiotherapy (including proton beam radiotherapy) or transcatheter arterial chemoembolization/infusion chemotherapy (TACE/TAI) tolerance was considered. If liver function and portal vein flow were poor due to tumor thrombi, only TAI with farmorubicin was administered. If TAI was not feasible, best supportive care was considered. After RH, TACE or TAI treatment was repeated until the residual tumor had completely disappeared on CT.

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Table I. *Patient characteristics.*

	RH	Control A	*p*-value	Control B	*p*-value
No. of patients	30	71		106	
Patient factors					
Age (yr)	60 (27-76)	65 (28-84)	**0.013***	63 (39-86)	**0.010***
Gender (M/F)	29/1	62/9	0.274§	90/16	0.119§
HBsAg positive	7	18	1.000§	14	0.250§
Anti-HCVAb positive	15	40	1.000§	74	0.052§
Total bilirubin (mg/dl)	0.9 (0.4-2.3)	0.8 (0.4-1.8)	0.390*	1.0 (0.4-2.2)	0.100*
Albumin (g/dl)	3.6 (2.8-4.3)	3.7 (2.8-4.7)	0.088*	3.5 (2.8-4.3)	0.351*
AFP (pg/ml)	540 (1.8-970,000)	71 (1.7-380,000)	0.126*	400 (1.7-350,000)	0.937*
Child-Pugh stage (A/B)	26/4	63/8	0.746§	83/23	0.438§
Okuda classification (I/II)	18/12	60/11	**0.010§**	84/22	0.054§
BCLC staging (B/C)	14/16	56/15	0.002§	74/32	0.029§
Tumor factors					
Size of main tumor (mm)	120 (45-200)	80 (45-220)	**0.001***	70 (45-150)	**<0.001***
Vascular invasion positive	16	15	**0.002§**	32	**0.029§**
Tumor extension in >50%	12	10	**0.007§**	11	**<0.001***

Values represent median (range). RH: reduction hepatectomy, HBsAg: hepatitis B surface antigen, Anti-HCVAb: anti-hepatitis C virus antibody, AFP: α-fetoprotein, BCLC staging: Barcelona Clinic Liver Cancer staging. Statistical significance was analyzed by Chi-square test§ and Mann-Whitney's *U*-test*.

Results

The patient characteristics are listed in Table I. As patients with similar background factors to those in RH patients were selected, no significant differences were found between the RH, control A and B groups. Cumulative 1-year survival rates for patients in RH, control A and B groups were 29%, 85% and 61%, and cumulative 3-year survival rates were 17%, 63% and 16%, respectively. Significant differences were found in survival between control group A and RH, and between control group A and control group B.

In cases where the main tumor was greater than 100 mm in diameter, cumulative 1- and 3-year survival rates for RH, control A and B groups were 32 and 26%, 82 and 45% and 31 and 0%, respectively. Significant differences were found between control A and RH, and between control A and control B group. In patients with vascular invasion, 1-year survival rates for RH, control A and B groups were 13%, 73% and 29%, while 3-year survival rates were 13%, 38% and 3%, respectively. In patients with tumor extension in >50% of the liver, 1-year survival rates for RH, control A and B groups were 50%, 90% and 11%, while 3-year survival rates were 42%, 60% and 0%, respectively. There was no significant difference between RH and control group A, but there was a significant difference between RH and control B (Figure 1). The characteristics of patients with tumor extension in >50% of the liver are shown in Table II. Total bilirubin was higher in control group B compared to RH group, while the other patient factors were similar between the three groups. Although larger HCCs were included in the RH group compared to control B group, the vascular invasion factor was similar.

Discussion

The background factors of patients treated with RH in our hospital were investigated first, using various prognostic scoring systems (Okuda stage, CLIP (10), JIS (11) , Tokyo score (12) and BCLC). There were no RH patients with Okuda stage III or BCLC stage A or D. As the RH patient distribution by the Okuda and BCLC staging systems was characteristic and not biased, they were used to unify the background factors of HCC patients. Several reports, after validation of the various prognostic staging systems for HCC, have indicated that the BCLC staging system provided the best independent prediction of survival (13, 14).

Patient factors were unified as much as possible, and two comparison groups were used (curative hepatectomy group and other local therapy group). After overall survival rates in each group had been compared, RH was definitively inferior to curative hepatectomy, and similar to other local therapies (including best supportive care).

However, although all patients in this study had multiple HCCs, three tumor factors (tumor size, vascular invasion and tumor extension) were further advanced in RH group compared to control A and B groups. These tumor factors were then estimated separately, and survival rates in each group with the same tumor condition were compared.

Table II. *Characteristics of patients with tumor extension in >50% of liver.*

	RH	Control A	*p*-value	Control B	*p*-value
No. of patients	12	10		11	
Patient factors					
Age (yr)	60 (27-74)	66 (45-70)	0.147*	61 (50-70)	0.389*
Gender (M/F)	12/0	9/1	0.455§	8/3	0.093§
HBsAg positive	3	2	1.000§	2	1.000§
Anti-HCVAb positive	4	4	1.000§	8	0.100§
Total bilirubin (mg/dl)	0.9 (0.5-1.2)	0.8 (0.5-1.0)	0.230*	1.4 (0.8-2.2)	**0.003***
Albumin (g/dl)	3.5 (2.8-4.0)	3.7 (3.0-4.3)	0.186*	3.6 (2.8-4.0)	0.687*
AFP (pg/ml)	6,400 (2.5-240,000)	290 (1.7-380,000)	0.210*	19,000 (3.5-92,000)	0.854*
Child-Pugh stage (A/B)	10/2	8/2	1.000§	6/5	0.193§
Okuda classification (I/II)	0/12	0/10		0/11	
BCLC staging (B/C)	5/7	7/3	0.231§	6/5	0.684§
Tumor factors					
Size of main tumor (mm)	160 (130-200)	130 (53-220)	0.079*	130 (90-150)	**0.006***
Vascular invasion positive	7	3	0.231§	5	0.684§

Values represent median (range). RH: reduction hepatectomy, HBsAg: hepatitis B surface antigen, Anti-HCVAb: anti-hepatitis C virus antibody, AFP: α-fetoprotein, BCLC staging: Barcelona Clinic Liver Cancer staging. Statistical significance was analyzed by Chi-square test§ and Mann-Whitney's *U*-test*.

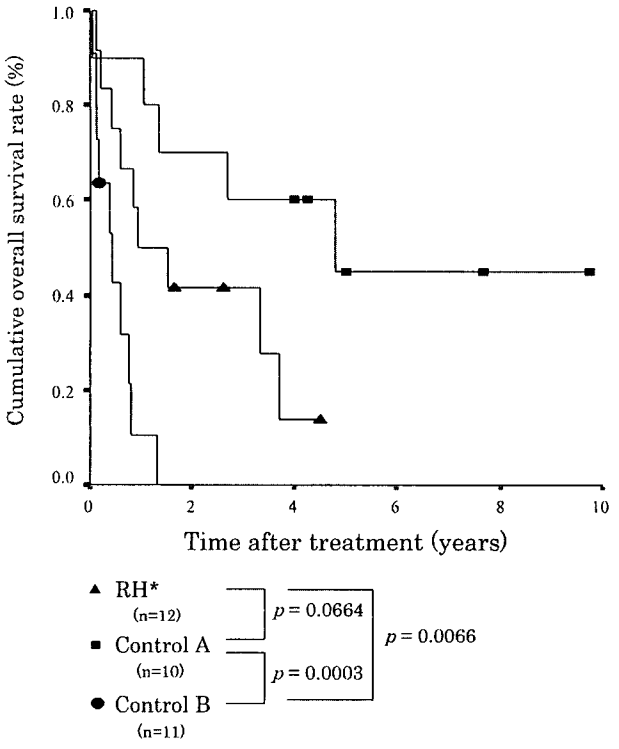

Figure 1. *Kaplan-Meier estimated survival curves according to treatment in patients with tumor extension in >50% of liver. *RH: reduction hepatectomy. Statistical significance was analyzed by log-rank test.*

After those comparisons, the survival benefit of RH for advanced multiple HCCs with tumor extension in >50% of the liver was found to be equivalent to that of curative hepatectomy and superior to that of other local therapy (including best supportive care). Since RH is intended to decrease the tumor volume in the liver, this result could suggest that RH is more effective for prolonged survival benefit if tumor extension in the liver is larger.

With regard to the effectiveness of RH for advanced HCC, Yamamoto *et al.* (4) reported that RH was effective in patients with fewer and smaller tumors left in the residual liver and no extrahepatic metastasis. However, only surgically treated patients were compared in the report. Wakabayashi *et al.* (5) compared two groups of patients (RH group and non-surgical group), and showed that RH had survival benefit. However, their background factors differed from ours, and the authors commented that unintended patient selection bias may have affected the results of the study. Although our evaluated patient factors were selected retrospectively, as shown in Table II, our treatment outcome was compared in groups selected to have equivalent factors, and, thus, our results were considered to be unbiased.

In conclusion, the present study suggested that RH for multiple advanced HCC with tumor extension in >50% of the liver might hold promise of survival benefit.

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バリアンス解析からみた肝切除クリニカルパスの適応

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原　著

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はじめに：クリニカルパスの視点で術後バリアンスが多いと考えられる肝切除術周術期管理において，当院では肝機能/肝切除量に応じた2種類の術後の輸液指示の異なるクリニカルパス（以下：パス）を作成し導入してきた経緯から，このパスのバリアンスやアウトカムを解析し，問題点およびその適応について検討した．**対象と方法**：2004年1月から12月までに当院で行われた肝切除例120例（胃癌および結腸/直腸癌同時肝切除症例を除く）のうち，パス適応となった115例を解析の対象とし，術後のバリアンス発生とアウトカム，術前肝機能・手術侵襲因子との相関関係を解析した．**結果**：パスが完遂された症例は115例中92例（80%）であった．術後平均在院日数はバリアンス発生のなかった全症例で平均9.0日であった．バリアンス発生に寄与する臨床的因子は疾患内訳，術式，手術時間，出血量，輸血の有無であった．また，術後2日目の経口摂取不良もバリアンス発生に関連していた．**考察**：2種類のパスのうち高度肝機能不良，大量肝切除症例への適応を想定して作られたパスは使用頻度も完遂率も低かった．そうした症例はパス適応外とするか，適応とするならば指標としては手術侵襲，特に手術時間5時間以内の症例が対象となるのではないかと考えられた．予定手術時間が5時間以上，かつ他の解析で求められた手術侵襲因子のカットオフ値も越えることが予想されるような場合はパスの適応外と考えられた．

緒　言

近年，消化器外科領域においてもクリニカルパス（以下，パス）の普及は目覚しく[1)2)]，治療の安全性の向上のみならず医療経済効果に貢献することが上げられている[3)~6)]．また，パス作成がこれまでの治療や検査そしてその経過を見直すきっかけとなり，不要と考えられる薬剤投与や検査の削減が実現され治療効率の向上も達成されている．しかし，手術侵襲が大きかったり，多彩な病態を呈する患者，腫瘍を有する疾患などにおける周術期ではバリアンスが多いためパス導入は遅れている[7)~9)]．

我々は，複雑な患者背景，肝機能低下を有し，術式・手術侵襲の差のある肝切除術に対し2003年から1年の試行期間を経て2004年より正式に医療用，患者用パスを作成・導入し，現在に至っている．今回，このパスのバリアンスやアウトカム解析を行い，肝切除術におけるパスの問題点およびその適応について検討した．

対象と方法

国立がんセンター東病院にて2004年1月から12月までに行われた肝切除症例120例（胃癌/結腸・直腸癌同時肝切除症例を除く）のうち，パスの適応とし115例を検討対象とした．胆道再建を要する4例と術前よりネフローゼを合併した症例1例はパスの適応外とした．経口摂取を肝切除術翌日より開始している．胆道再建（消化管再建）を要する肝切除症例については経口摂取開始を遅らせるためパス適応外とした．

肝切除パスの導入に際し工夫点として，複雑な患者背景や肝機能，また手術術式や手術侵襲の程

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