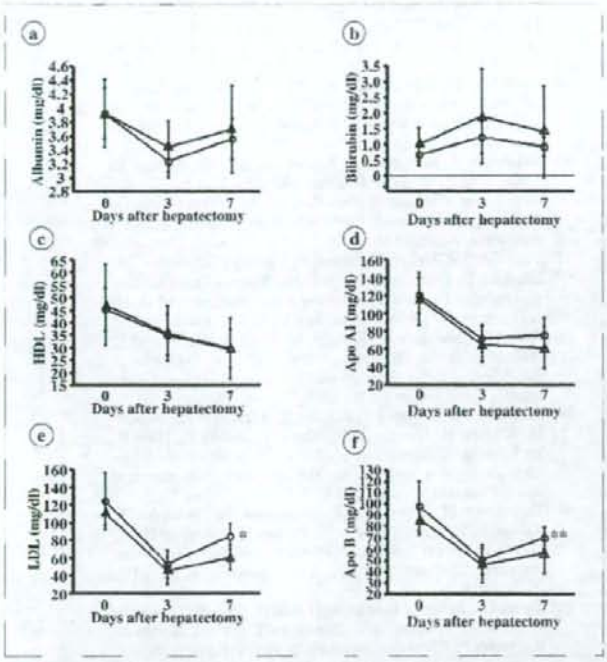

FIGURE 1 Albumin (a), bilirubin (b), HDL (c), ApoAI (d), LDL (e), and ApoB (f) levels before and after hepatectomy. Bars show standard deviations. Circles (°) show the SLC group and triangles (-) show the AR group. Asterisk (*) shows significant differences ($P < 0.01$) and double asterisk (**) shows significant differences ($P < 0.05$).

to prevent unnecessary bleeding. To reverse it would create certain bleeding from the liver parenchyma and need blood inflow occlusion to control bleeding. This suggests that there are learning steps for achieving the maximal SLC benefit in liver surgery.

Evaluation of liver function after thermal ablation

It is thought that thermal ablation leaves certain necrotic areas beneath the liver transection area, perhaps hampering the recovery of liver function after hepatectomy. Recovery of hepatic function is difficult to evaluate after hepatectomy, because classical hepatic functional markers such as albumin and PT are modified by each transfusion of either albumin or plasma. Bilirubin levels are normalized within several days after uneventful hemihepatectomy in the case of the normal liver. We have reported that serum LDL and ApoB levels can be markers to determine recovery of liver function within 7 days after hepatectomy (20). Full recovery of serum HDL and ApoAI levels is delayed to about 2 weeks after hepatectomy (19). Recovery of hepatic function after hepatectomy is affected by both the type of hepatectomy and the severity of the liver disease. Serum lipid and Apo levels could be markers of recovery of hepatic function in patients who receive the same type of hepatectomy with the same pathological background of the liver. In our study, we investigated noncirrhotic cases who received hemihepatectomy. In this setting, we could precisely evaluate liver functions in paired groups after hepatectomy.

It is exceedingly interesting that recovery of liver function in the SLC group seemed to be much faster than in the AR group, as we saw at 7 days after hepatectomy with high levels of LDL and ApoB in the SLC group. One of the reasons might be a difference in subclinical liver function between the groups. Although there was no significant difference in the hyarulonate and type IV collagen levels between the groups, their average in the AR group was higher than in the SLC group. This substantial liver fibrosis may have hampered the recovery of hepatic function in the AR group. Another reason could be that there are some thermal benefits in the recovery of hepatic function in the SLC group. An experimental study revealed that heat shock protein (HSP) protects against cell damage in ischemic tissue (23). In addition, hyperthermia induces HSP protein in the liver and HSP might relieve heat injury (24). It would be interesting to further investigate if HSP induced in the liver after thermal ablation could facilitate the recovery of hepatic function. The other reason could be that the short warm ischemic time during hepatectomy in the SLC group might reduce ischemic injury. In any case, we found better recovery of hepatic function with the SLC method rather than a harmful effect of heat injury after major hepatectomy.

In conclusion, we investigated patients who received major hepatectomy and compared recovery of hepatic function between the AR method and SLC method. SLC reduced warm ischemic time during hepatectomy and LDL and ApoB was recovered faster than with the AR method. Our results suggested that heat effect using SLC during hemi-hepatectomy could facilitate recovery of liver function rather than impede it. However, our study only provides preliminary results from a retrospective small number of study; therefore, further prospective large studies are needed. In addition, basic study is needed to investigate the mechanism of the heat effect on hepatic function.

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ORIGINAL ARTICLE

Prognostic Impact of Surgical Complications and Preoperative Serum Hepatocyte Growth Factor in Hepatocellular Carcinoma Patients After Initial Hepatectomy

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Abstract
Introduction The relationship between postoperative complications and survival after hepatectomy is not completely understood. The purpose of this study was to determine if surgical complications would have a prognostic impact and to identify any difference of the prognostic factors between a complication group and complication-free group for hepatocellular carcinoma (HCC) patients after initial hepatectomy.
Patients and Methods One hundred consecutive HCC patients were analyzed in this study. Operative variables and liver functional markers were compared between the complication group and complication-free group. The diagnostic accuracy for predicting complications was evaluated by the receiver operating characteristic (ROC) curve. The Kaplan–Meier method with log-rank test was employed for survival analysis. Univariate and multivariate analyses were performed to identify the prognostic factors in each group.
Results and discussion A total of 45 complications in 32 patients were observed according to the modified Clavien classification. The albumin, γ-glutamyl transferase, choline esterase, indocyanine green retention rate at 15 min ($ICGR_{15}$), hyaluronic acid, prealbumin, hepatocyte growth factor (HGF), HH15, and LHL15 levels before hepatectomy, operative time, and blood loss were significantly different between the two groups. Multivariate analysis revealed that γ-glutamyl transferase, $ICGR_{15}$, and HGF were independent risk factors for postoperative complications. The values of the areas under the ROC curve for predicting complications proved the significance of the predictions. Although the recurrence-free survival rates were not significantly different, the overall survival rates were significantly different between the two groups. Univariate and multivariate analyses for the overall survival rate showed that the stage of the HCC and HGF for the complication group and tumor size for the complication-free group were independent prognostic factors for overall survival.
Conclusion Postoperative surgical complications could have a prognostic impact on overall survival in HCC patients after initial hepatectomy. Serum HGF could be a factor connected to complications and survival in this group.

Keywords Hepatectomy · Hepatocyte growth factor · Hepatocellular carcinoma · Complication · Prognosis

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Introduction

The incidence of hepatocellular carcinoma (HCC) has been increasing internationally due to epidemic viral hepatitis.[1,2] Liver resection is one of the best curative therapies for HCC patients who maintain good liver function,[1,2] and assessment of liver functions before surgery is important to avoid liver dysfunction or liver failure.[3–5] Many indicators have been used for the assessment of liver function such as the Child–Pugh score,[3] indocyanine green retention rate at

15 min ($ICGR_{15}$),[3] ^{99m}Tc-galactosyl serum albumin (GSA),[4] and serum hyaluronic acid (HA) levels.[5] Knowledge of these preoperative evaluations, in addition to the improvement of surgical techniques and devices, helps surgeons to perform safe hepatectomy in modern surgery. The mortality in the 1980s was reported to be approximately 10% for major hepatectomy, but has now been reduced to only a few percent.[6,7]

Although the mortality rate in liver surgery has decreased, surgical complications may be inevitable to some degree. If the operative procedure and perioperative management with an appropriate surgical plan are completed without errors, surgical complications should become minimal. In this circumstance, surgical complications could be mostly related to the host condition. Viral-associated HCC develops in the process of disease progression such as chronic hepatitis and liver cirrhosis[8,9] when liver function deteriorates in parallel. Therefore, HCC patients are vulnerable to complications associated with surgical stress.

Many perioperative variables, such as tumor factors (tumor size, number of tumors, extension of the tumor, and vascular invasion), clinical factors (age, liver damage, and α-fetoprotein [AFP]), and operative factors (surgical curability and margin), are related to recurrence and the survival rate after hepatectomy.[10] The cause of death in HCC patients is usually either cancer-related or liver failure-related. Good liver function has the potential to prolong survival due to more chances to receive additional salvage therapy.[11] Therefore, liver function may play an important role in predicting not only postoperative complications but also survival after hepatectomy. However, the relation between postoperative complications and survival after hepatectomy is not completely understood.

Hepatocyte growth factor (HGF) is found in the sera of patients with fulminant liver failure[12] and promotes hepatocyte proliferation, including that of hepatocellular carcinoma cells.[13] Clinically, HGF levels are well-correlated with the worsening of liver disease.[8,9] High HGF levels in the cirrhotic liver correlate with the presence of hepatocellular carcinoma and overall prognosis.[9] We have also reported that the preoperative HGF level correlates with postoperative liver dysfunction.[5] Therefore, HGF is very important not only for mitogenic activity but also as a clinical indicator to predict cancer development, the severity of liver disease, and liver dysfunction after hepatectomy. However, the significance of HGF in predicting postoperative complications in liver surgery has not been clarified yet.

We surveyed patients who had complications after initial hepatectomy and compared them to patients who were discharged on schedule to identify risks for complications after hepatectomy. Furthermore, we hypothesized that the deteriorated patient condition might be a major reason for complications and result in a different clinical prognosis. The aim of this study was to identify prognostic factors among patients who had complications and those who were complication-free after initial hepatectomy in 100 consecutive HCC patients.

Patients and Methods

Patients

Between January 2001 and December 2005, 100 hepatocellular carcinoma patients who underwent hepatectomy were enrolled in this study with informed consent. Mortality was defined as any death in the hospital within 90 days after operation. Postoperative complications were defined and classified by the modified Clavien classification system.[14] Briefly, grade I was any deviation from the normal postoperative course without any special treatment. Grade II was requiring pharmacological treatment with drugs. Grade III was requiring surgical or radiological intervention with (IIIb) or without (IIIa) general anesthesia. Grade IV was a life-threatening complication involving single (IVa) or multiple (IVb) organ dysfunction. Grade V was the death of the patient. Of the complications ranked grade IV or higher, liver failure/insufficiency was defined as a serum bilirubin concentration of more than 10 mg/dL for more than 2 days. Portal vein thrombosis and pulmonary effusion were diagnosed either by ultrasound sonography or computed tomography with enhancement. Pneumonia was diagnosed either by respiratory symptoms with X-ray examination or proof of bacteria. Venous thrombosis was defined by a sudden respiratory distress symptom with decreased peripheral oxygen saturation regardless of proof of a thrombus. Angina pectoris/acute myocardial infarction was defined as chest pain and by electrocardiographic examination. Renal insufficiency was defined by oliguria (less than 400 mL/day) with sustained serum creatine elevation of more than 1.1 mg/dL. Although no mechanical ileus that required nasointestinal tube drainage occurred, paralytic ileus was observed with oral intake of less than 500 mL/day for more than 3 days. Gastrointestinal bleeding was diagnosed by endoscopic examination. Wound infection/dehiscence was defined as any wound that split open regardless of proof of bacteria. Ascites was defined as fluid discharge of more than 300 mL/day for more than 3 days.

We divided the patients into two groups. The complication group consisted of 32 patients who had complications of any grade during the hospital stay. The complication-free group consisted of 68 patients who were discharged within 14 days after hepatectomy. The study design conformed to

the ethical guidelines of the Declaration of Helsinki and obtained informed consent with individual signature prior to registry.

Assessment of Clinical and Operative Variables

Routine laboratory tests conducted before hepatectomy included those for $ICGR_{15}$, hyaluronic acid as a liver fibrotic marker, prealbumin as a rapid turnover protein, HGF, AFP, PIVKAII, and GSA (HH15, LHL15). Intraoperative data and any complications during hospital stays were recorded. Tumor size, number, and vascular invasion were recorded by pathological examinations. All laboratory tests were conducted in the early morning on the day of assessment.

Surgical Procedure

All liver resections were basically performed with Pringle maneuver techniques after more than 300 mL of intraoperative bleeding. No hepatic flow was controlled if intraoperative bleeding was less than 300 mL. A Cavitron ultrasonic aspirator (CUSA) was used for liver parenchymal dissection. Either an argon laser beam coagulator or a saline-linked monopolar electric cautery was used to achieve hemostasis. Antibiotics were administered at 30 min before laparotomy and every 3 h during the operation. Absorbable sutures (Vicryl or PDS, Johnson & Johnson Gateway, Piscataway, NJ, USA) were used for all sutures and ties except for skin closure. Skin was closed with either nylon sutures or a skin stapler. Periwound skin was washed with 500 mL of warm saline before skin closure. Either a closed-type subphrenic or hepatoduodenal drain was placed after hepatectomy and removed 2 or 3 days later.

Statistical Analysis

For statistical analyses, demographic and perioperative laboratory tests were extracted from the database and the differences between the groups were compared using the chi-square test followed by a post hoc 2×2 Fisher exact test, when needed. Logistic regression analysis was used to identify the most relevant risks of complication. Factors determining overall survival were assessed using the Kaplan–Meier method with comparison of the log-rank test and univariate or multivariate analysis using the Cox proportional hazards regression model. The calculations were performed using the StatView 5.0 software package (Abacus Concepts, Berkeley, CA, USA) or SPSS 15.0 (SPSS, Chicago, IL, USA). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) was determined using the MedCalc software package (Version 8.0.1.0, Mariakerke, Belgium). All results are expressed as the mean values± standard deviations (SD). $p<0.05$ was considered to be statistically significant.

Results

In our 100 consecutive hepatectomies for HCC, 45 complications were observed in 32 patients, although 38 of the complications in 26 patients were minor ones (Table 1). Serious grade V complications consisted of two liver failures, one myocardial infarction, and one gastrointestinal hemorrhage. Although one patient recovered after intensive care, he was classified as having grade IVb liver failure and renal failure. Clinical and operative variables were compared between the two groups (Table 2). Although age, sex, the type of virus, pathological background, stage of the HCC, bilirubin, prothrombin time, tumor markers, tumor size, number of tumors, vascular invasion, and type of hepatectomy were not significantly different between the groups, the albumin ($p=0.010$), γ-glutamyl transferase ($p=0.002$), choline esterase ($p=0.008$), $ICGR_{15}$ ($p=0.007$), HA ($p=0.003$), prealbumin ($p=0.004$), HGF ($p=0.005$), HH15 ($p=0.001$), and LHL15 ($p=0.021$) levels before hepatectomy, operative time ($p=0.003$), and blood loss ($p=0.001$) were significantly different. Multivariate analysis revealed that γ-glutamyl transferase ($p=0.002$), $ICGR_{15}$ ($p=0.047$), and HGF ($p=0.003$) were independent risk factors for postoperative complications in our series (Table 3). The area under the ROC curve (AUC) was calculated for three factors (Fig. 1) and all of them were significantly different (γ-glutamyl transferase: $p=0.005$; $ICGR_{15}$: $p=0.002$; HGF: $p<0.001$).

The recurrence-free survival curve and overall survival curve are shown in Fig. 2. Although the recurrence-free survival was not significantly different between the two groups ($p=0.108$), the overall survival probability was significantly different ($p=0.036$). Mean overall survival times were 58.94±4.14 months in the complication-free group and 39.07±5.75 months in the complication group. Univariate (Table 4) and multivariate (Table 5) analyses were performed to identify significant impacts on overall survival among clinical and operative variables in each group independently. Univariate analysis using the Cox proportional hazards model in the complication group revealed that the pathological background ($p=0.031$), stage of the HCC ($p=0.004$), HGF ($p=0.015$), AFP ($p=0.004$), PIVKAII ($p=0.005$), tumor size ($p=0.004$), vascular invasion ($p=0.041$), and blood loss ($p=0.006$) were significant risk factors in this group. On the other hand, in the complication-free group, albumin ($p=0.024$), $ICGR_{15}$ ($p=0.001$), prealbumin ($p=0.001$), tumor size ($p=0.001$), and blood loss ($p=0.018$) were significant risk factors. Multivariate analysis of these factors in the complication group showed that the stage of

Table 1 Postoperative Complications in 32 Patients

Complications	Total number	Grade of surgical complication						
		I	II	IIIa	IIIb	IVa	IVb	V
Liver/biliary								
Liver failure/insufficiency	4					1	1	2
Bile leak	2			2				
Portal vein thrombosis	2		2					
Pulmonary								
Pleural effusion (symptomatic)	6	2	2	2				
Pneumonia	2		2					
Cardiovascular								
Venous thrombosis	2		2					
Angina pectoris/myocardial infarction	1							1
Genitourinary								
Renal insufficiency/failure	2		1				1	
Gastrointestinal								
Ileus	3			3				
Gastrointestinal hemorrhage	2			1				1
Miscellaneous								
Wound infection/dehiscence	8	6	2					
Ascites	11	4	5	2				
Total number (complications/patients)	45/32	38/26				7/6		

Grades of surgical complications are according to modified Clavien classification

Table 2 Clinical and Operative Variables in HCC Patients After Initial Curative Hepatectomy

Variables	Complication (n=32)	Complication-free (n=68)	p value
Age (years)	64.69±8.65	61.87±10.45	0.189
Sex (male/female)	26:6	50:18	0.391
Etiology (B/C/NBNC)	18:13:1	43:19:6	0.101
Background (CH/LC/N)	9:21:2	27:32:9	0.199
Stage (I/II/III/IV)	5:10:12:5	17:22:20:9	0.707
Albumin (g/dL)	3.73±0.43	3.95±0.44	0.010*
Bilirubin (mg/dL)	0.92±0.39	0.84±0.36	0.243
Prothrombin time (%)	93.19±17.44	98.59±12.15	0.081
γ-Glutamyl transferase (IU/L)	140.05±108.36	87.54±81.15	0.002*
Choline esterase (IU/L)	193.74±71.13	233.25±79.97	0.008*
$ICGR_{15}$ (%)	18.32±9.14	13.73±8.73	0.007*
Hyaluronic acid (ng/mL)	264.25±251.65	162.12±142.61	0.003*
Prealbumin (mg/dL)	13.96±6.79	18.75±7.76	0.004*
HGF (ng/mL)	0.43±0.22	0.33±0.14	0.005*
AFP (ng/mL)	5,254.56±17,866.77	2,164.15±11,688.14	0.236
PIVKAII (mAU/mL)	4,718.72±16,174.82	4,955.79±19,361.02	0.947
HH15	0.652±0.095	0.593±0.074	0.001*
LHL15	0.902±0.055	0.924±0.037	0.021*
Tumor size (cm)	4.69±3.31	4.54±3.44	0.820
Tumor number	1.97±1.44	1.69±1.21	0.267
Vascular invasion (negative/positive)	16:16	36:32	0.783
Type of resection (Hr0 or HrS/Hr1/Hr2/Hr3)	19:4:6:3	42:15:9:2	0.063
Operation time (min)	425.91±279.06	298.23±96.01	0.003*
Blood loss (mL)	1,308.78±1,474.34	562.17±503.54	0.001*

HCC: hepatocellular carcinoma, *B*: HBV, *C*: HCV, *NBNC*: non-B and non-C hepatitis, *CH*: chronic hepatitis, *LC*: liver cirrhosis, *N*: normal liver, $ICGR_{15}$: indocyanine green retention rate at 15 min, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II, *HH15*: clearance index, *LHL15*: receptor index, *Hr0*: partial resection, *HrS*: subsectionectomy, *Hr1*: sectionectomy, *Hr2*: hemihepatectomy, *Hr3*: trisectionectomy

*$p<0.05$

Table 3 Logistic Regression Analysis for Contributing to Risk of Complications After Liver Resection in HCC Patients

Variables		Odds ratio	95%CI	*p* value
Albumin (g/dL)	>4.0	1	0.245–5.929	0.819
	≤4.0	1.204		
γ-Glutamyl transferase (IU/L)	<100	1	2.216–33.278	0.002*
	≥100	8.587		
Choline esterase	≥200	1	0.092–2.736	0.425
	<200	0.502		
$ICGR_{15}$ (%)	<10	1	1.026–35.500	0.047*
	≥10	6.034		
Hyaluronic acid (ng/mL)	<130	1	0.026–1.097	0.062
	≥130	0.168		
Prealbumin (mg/dL)	≥15	1	0.591–11.788	0.204
	<15	2.639		
HGF (ng/mL)	<0.35	1	2.392–65.979	0.003*
	≥0.35	12.562		
HH15	<0.60	1	0.210–4.315	0.951
	≥0.06	0.953		
LHL15	≥0.9	1	0.665–16.331	0.144
	<0.9	3.295		
Operation time (min)	<300	1	0.704–11.218	0.143
	≥300	2.810		
Blood loss (mL)	<600	1	0.125–2.437	0.432
	≥600	0.551		

HCC: hepatocellular carcinoma, *$ICGR_{15}$*: indocyanine green retention rate at 15 min, *HGF*: hepatocyte growth factor, *HH15*: clearance index, *LHL15*: receptor index
*$p<0.05$

the HCC ($p=0.036$) and HGF ($p=0.006$) were significant independent risk factors for overall survival, but in the complication-free group, tumor size ($p=0.015$) was the only significant independent risk factor for overall survival.

Discussion

We showed in this study that perioperative complications could be risk factors indicative of overall prognosis. Among

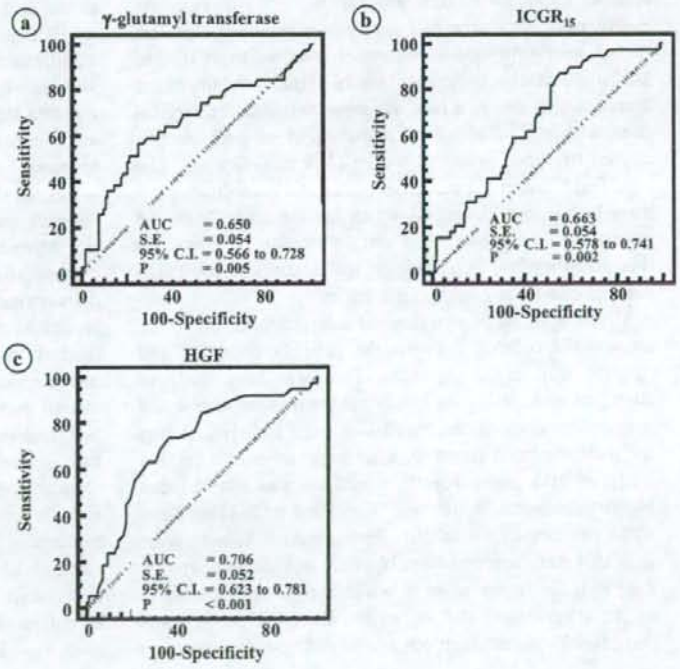

Figure 1 ROC curves of γ-glutamyl transferase (**a**), $ICGR_{15}$ (**b**), and HGF (**c**) for predicting complications after initial hepatectomy for HCC patients. *AUC* area under the ROC curve, *S.E.* standard error, *C.I.* confidence interval. $p<0.05$ was considered to be significant.

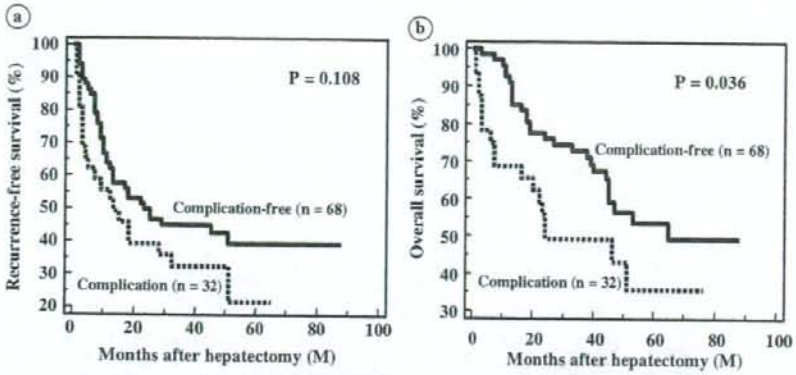

Figure 2 Recurrence-free survival curve (**a**) and overall survival curve (**b**) after initial hepatectomy for 100 HCC patients in the complication group (n=32, *dotted line*) and complication-free group (n=68, *solid line*). Mean recurrence-free times in the complication group and the complication-free group were 25.64±4.69 and 43.26±4.74 months, respectively (p=0.108). Mean overall survival times in the complication group and the complication-free group were 39.07±5.75 and 58.94±4.14 months, respectively (p=0.036).

the clinical and operative variables, γ-glutamyl transferase, $ICGR_{15}$, and HGF were independent risk factors for postoperative complications. Furthermore, HGF was an independent prognostic factor in the complication group in addition to the stage of the HCC. On the other hand, tumor size was the only independent prognostic factor in the complication-free group. Our study indicated a close relation between postoperative complications and overall survival in HCC patients after initial hepatectomy.

Morbidity and mortality after hepatectomy have been reduced by recent surgical procedures.[6,11,15] However, the quality of postoperative complications is still being debated. In fact, morbidity due to hepatectomy varied from 10% to 50% in a past study.[16] The variability of the morbidity in the literature was due to a lack of proper definition of surgical complications.[17] Recently, a definition of surgical complications has been proposed with a clear classification. The modified Clavien classification of surgical complications is a well-organized system in which any deviation from the normal perioperative course can be recorded.[14] Based on this classification, bias with regard to surgical complications in our study could be minimized.

Under minimal bias of surgical complications, morbidity reflects the balance between the patient's condition and surgical skill or management. The large case study of Blumgart and colleagues found that the number of resected segments and estimated blood loss were high risk factors for morbidity and mortality after hepatectomy.[18] Another study of 100 major hepatic resections also showed that blood transfusion, which was associated with blood loss, was a risk factor for morbidity after surgery.[19] These reports indicated that there was more bleeding and longer operation time in more severe cases in which the patient's condition might deteriorate and become vulnerable to surgical complications. Although our results showed that operation time and blood loss lost significance in multivariate analysis, in univariate analysis they were significantly different, which was partly consistent with previous reports. Furthermore, the hepatic background in the complication-free group tended to be less cirrhotic, which could make it easier control bleeding than in the complication group, although there was no significant difference between the groups. We, however, could not rule out the possibility that we employed less-invasive hepatic resection in cirrhotic cases and more aggressive hepatic resection in normal cases. As long as we conducted our routine liver resection for HCC patients, the intrinsic patient condition was a more significant risk factor for postoperative complications in our 100-case series than operative variables. Therefore, it is possible that we could not have prevented most postoperative complications in our series even if our surgical approach were reconsidered to reduce morbidity. In other words, postoperative complications are dependent on the patient's condition and cannot be totally avoided.

Furthermore, our study showed the prognostic impact of postoperative complications for HCC patients, although disease-free survival was not significantly different. The prognosis of the HCC patient after hepatectomy partially depends on the liver function,[11] which is associated with increased opportunities for various treatments. The longer overall survival in the complication-free group indicated that fundamental liver function in this group was better than that in the complication group. In fact, comparison of clinical variables between the two groups indicated that liver function in the complication-free group was much better than that of the complication group. Therefore, the survival difference between the groups was most likely due to the difference of fundamental liver function. If surgical complications randomly occurred due to technical errors, liver functions should have been similar between the

Table 4 Univariate Analysis for Clinical Factors Contributing to Overall Survival After Liver Resection in HCC Patients

Variables		Complication (n=32)				Complication-free (n=68)			
		n	Hazard ratio	95%CI	p value	n	Hazard ratio	95%CI	p value
Age (years)	<65	13	1	0.634–4.828	0.280	35	1	0.438–2.294	0.994
	≥65	19	1.749			33	1.003		
Sex	Men	26	1	0.466–4.567	0.516	50	1	0.262–2.273	0.638
	Women	6	1.459			18	0.772		
Etiology (NBNC, B/C)	N, B	19	1	0.460–3.284	0.681	49	1	0.279–1.801	0.469
	C	13	1.229			19	0.709		
Background (N, CH/LC)	N, CH	11	1	1.085–5.552	0.031*	36	1	0.593–3.870	0.386
	LC	21	2.455			32	1.514		
Stage (I, II/III, IV)	I, II	15	1	1.801–22.972	0.004*	39	1	0.990–6.181	0.052
	III, IV	17	6.433			29	2.474		
Albumin (g/dL)	≥4.0	9	1	0.412–4.086	0.656	34	1	1.143–6.850	0.024*
	<4.0	24	1.297			34	2.798		
Bilirubin (mg/dL)	<1.0	24	1	0.559–4.705	0.373	51	1	0.738–4.128	0.205
	≥1.0	8	1.622			17	1.745		
Prothrombin time (%)	≥90	20	1	0.590–4.273	0.360	52	1	0.560–3.390	0.485
	<90	12	1.588			16	1.378		
γ-Glutamyl transferase (IU/L)	<100	12	1	0.799–7.845	0.115	52	1	0.615–3.447	0.392
	≥100	20	2.504			16	1.457		
Choline esterase (IU/L)	≥200	17	1	0.519–3.761	0.508	46	1	1.933–10.418	0.001*
	<200	15	1.397			22	4.488		
$ICGR_{15}$ (%)	<10	5	1	0.491–28.439	0.203	42	1	0.957–6.314	0.062
	≥10	27	3.736			26	2.457		
Hyaluronic acid (ng/mL)	<130	11	1	0.712–8.786	0.152	39	1	1.868–11.168	0.001*
	≥130	21	2.501			29	4.568		
Prealbumin (mg/dL)	≥15	12	1	0.856–10.588	0.585	45	1	2.075–12.015	0.001*
	<15	20	3.011			23	4.993		
HGF (ng/mL)	<0.35	20	1	1.424–29.258	0.015*	50	1	0.937–5.288	0.069
	≥0.35	12	6.456			18	2.226		
AFP (ng/mL)	<100	20	1	1.615–12.671	0.004*	47	1	0.499–2.786	0.707
	≥100	12	4.524			21	1.179		
PIVKAII (mAU/mL)	<100	16	1	1.766–24.099	0.005*	39	1	0.657–3.384	0.339
	≥100	16	6.524			29	1.491		
HH15	<0.60	13	1	0.335–5.063	0.703	35	1	0.336–3.028	0.987
	≥0.06	19	1.301			33	1.009		
LHL15	≥0.9	13	1	0.134–2.106	0.368	54	1	0.398–5.317	0.571
	<0.9	19	0.532			14	1.454		
Tumor size (cm)	<5	19	1	1.645–15.717	0.004*	53	1	2.137–12.790	0.001*
	≥5	13	5.085			13	5.228		
Tumor number	Single	18	1	0.834–7.505	0.101	40	1	0.900–5.267	0.084
	Multiple	14	2.502			28	2.177		
Vascular invasion	Negative	16	1	1.052–10.804	0.041*	36	1	0.831–4.892	0.122
	Positive	16	3.371			32	2.016		
Type of resection (Hr0,S/Hr1–3)	Hr0,S	19	1	0.545–3.974	0.446	42	1	0.369–2.726	0.995
	Hr1–3	13	1.471			26	1.003		
Operation time (min)	<300	12	1	0.764–7.516	0.134	40	1	0.198–2.107	0.468
	≥300	20	2.396			28	0.645		
Blood loss (mL)	<600	13	1	1.795–35.245	0.006*	44	1	1.146–10.853	0.018*
	≥600	19	7.953			24	3.526		

HCC: hepatocellular carcinoma, *B*: HBV, *C*: HCV, *NBNC*: non-B and non-C hepatitis, *CH*: chronic hepatitis, *LC*: liver cirrhosis, *N*: normal liver, $ICGR_{15}$: indocyanine green retention rate at 15 min, *HGF*: hepatocyte growth factor, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II, *HH15*: clearance index, *LHL15*: receptor index, *Hr0*: partial resection, *HrS*: subsectionectomy, *Hr1*: sectionectomy, *Hr2*: hemihepatectomy, *Hr3*: trisectionectomy

*p<0.05

Table 5 Multivariate Analysis for Contributing to Overall Survival After Liver Resection in HCC Patients

Variables		Hazard ratio	95%CI	*p* value
Complication (n=32)				
Stage (I, II/III, IV)	I, II	1	1.301–3896.771	0.036*
	III, IV	72.212		
HGF (ng/mL)	<0.35	1	4.146–5421.990	0.006*
	≥0.35	149.935		
AFP (ng/mL)	<100	1	0.119–157.582	0.423
	≥100	4.335		
PIVKAII (mAU/mL)	<100	1	0.252–18.559	0.482
	≥100	2.161		
Tumor size (cm)	<5	1	0.009–2.414	0.179
	≥5	0.147		
Blood loss (mL)	<600	1	0.650–106.304	0.103
	≥600	8.312		
Complication-free (n=68)				
Albumin (g/dL)	≥4.0	1	0.278–10.507	0.562
	<4.0	1.710		
Choline esterase (IU/L)	≥200	1	0.074–6.846	0.766
	<200	0.710		
Hyaluronic acid (ng/mL)	<130	1	0.745–18.819	0.109
	≥130	3.744		
Prealbumin (mg/dL)	≥15	1	0.412–38.993	0.232
	<15	4.008		
Tumor size (cm)	<5	1	1.377–21.299	0.015*
	≥5	5.416		
Blood loss (mL)	<600	1	0.255–6.916	0.736
	≥600	1.328		

HCC: hepatocellular carcinoma, *CI*: confidence interval, *HGF*: hepatocyte growth factor, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II
*$p<0.05$

groups. In such a case, no survival impact would be observed and our results could not have been obtained. Therefore, complications could become a prognostic factor as long as the surgical technique and management are properly conducted.

In the complication group, HGF was one of the independent prognostic factors besides the stage of the disease. The serum HGF level represents the severity of clinical liver disease.[8,9] HGF is correlated with pathological fibrosis and the presence of hepatocellular carcinoma.[9] Severe pathological fibrosis could be a cause of perioperative complications and the presence of HCC leading to a poor prognosis. In the complication group, high HGF indicated disease deterioration with poor liver function. Additional therapy for recurrence in this group was difficult due to poor liver function. Basically, HGF function in the normal liver could play an important role for hepatocyte survival and tissue remodeling.[20] However, our study and others seem to show controversial results in the clinical setting. This indicates that the liver is desensitized to HGF signals for some reason when liver disease deteriorates. Therefore, a high HGF level in a diseased patient does not have a biological effect on the diseased liver. This suggests that the function of c-*met*, as an HGF receptor, may decrease or the activity of HGF itself may be reduced. Receptor abnormality[21] and the inactive form of HGF[22] are considered to be potential mechanisms of the HGF elevation in liver disease, including HCC. In some way, the mechanism quenching HGF from the serum fails and the signals never go through the hepatocytes. On the other hand, cancer cells, apart from the normal hepatocytes, might respond to mitogenic activity of HGF, which might promote disease progression and affect overall survival.

Conclusion

We surveyed 100 consecutive HCC patients who had initial hepatectomy. Postoperative complications were recorded with the modified Clavien classification. We have shown that postoperative surgical complications could be a prognostic factor for overall survival in our study. Furthermore, a high serum HGF level could be a risk factor for complications and overall survival in this group, although we observed no difference of recurrence-free time between the groups due to the small number of subjects on this study. A large number of multiple center trials should be designed to clarify the prognostic value of the preoperative HGF level in the future.

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大血管内進展を伴う進行再発肝細胞癌に対する外科治療

Surgical treatment for recurrent hepatocellular carcinoma with invasion to major vessels

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●要旨●門脈や下大静脈内に腫瘍栓を形成する高度進行肝細胞癌（肝癌）は大型肝癌が多く，また，再発例では癒着や解剖学的な偏位がみられる場合があるので，術前に遠隔転移を含めた肝癌進展範囲と外科解剖を十分把握しておく。門脈腫瘍栓例では門脈本幹と左右1次分枝を遮断後，腫瘍栓を摘出する。下大静脈内腫瘍栓が右心房内に進展している場合は人工心肺下に，肝上部下大静脈内に腫瘍栓が存在し，その頭側にテーピングが可能な場合，全肝血流遮断（THVE）下に腫瘍栓を摘出する。肝静脈流入部尾側で下大静脈にテーピングが可能であれば，下大静脈のクランプのみで腫瘍栓を摘出し得る。大血管内進展を伴う進行再発肝癌の手術は侵襲の大きな治療であるので，慎重な手術適応決定と心臓外科などとの協力体制が重要である。

● key words：肝細胞癌，門脈腫瘍栓，下大静脈内腫瘍栓，人工心肺，全肝血流遮断（total hepatic vascular exclusion；THVE）

はじめに

肝細胞癌（肝癌）は進行すると門脈に浸潤，腫瘍栓（Vp）を形成，しばしば門脈本幹や反対側の肝内門脈枝に進展する。また，肝静脈に浸潤，形成された腫瘍栓（Vv）が下大静脈内に進展し，時にその腫瘍栓が右心房内に達することがある。初発例のみならず，肝癌切除後の肝内再発例においても再発部位によっては早期に門脈腫瘍栓や下大静脈内腫瘍栓を形成する。さらに，近年，マイクロウェーブ凝固療法やラジオ波焼灼術などの治療後に急速に門脈や肝静脈内に進展し，腫瘍栓を形成する症例も経験されるようになった。

このような大血管内に進展した局所高度進行肝癌の手術適応は慎重でなければならないが，症例によってはほぼ完全に切除できる場合や，術後リザーバー動注や5-FU・インターフェロン療法の併用などにより長期生存が期待できる症例がみられることから，再発例であっても外科的治療が適応となる症例がみられる。

本稿ではこのような大血管内進展を伴う進行再発肝癌に対する外科的治療手技や問題点について概説する。

大血管内進展を伴う進行再発肝癌に対する手術の注意点

一般に肝切除後再発例に対する再肝切除においては，肝切離部や肝門部の高度な癒着や解剖学的偏位がしばしばみられる。そのため，術前の画像診断において肝癌の進展範囲や主要血管との位置関係をしっかりと把握しておくことが重要である。Vp_3やVp_4症例では術前肝内転移巣や食道静脈瘤の検索を行う。また，下大静脈内腫瘍栓を伴う肝癌症例は容易に肺転移をきたすため，肺転移を含めた遠隔転移がないことを術前に確認する。大血管内進展を伴う症例では一般に大型肝癌の場合が多いので，十分な視野を得るため，正中切開に加えて両肋弓下切開を行う。肝静脈根部の確保が困難な場合は躊躇なく右第8あるいは第9肋間へと切開を延長し，開胸操作を加える。術中，逐次超音波検査を行い，腫瘍の位置と脈管の走行を確認しつつ手術を進め，脈管や周囲臓器の不用意な損傷を避ける。マイクロウェーブ凝固療法やラジオ波焼灼術などの局所治療や肝動脈塞栓術などが繰り返し行われていた場

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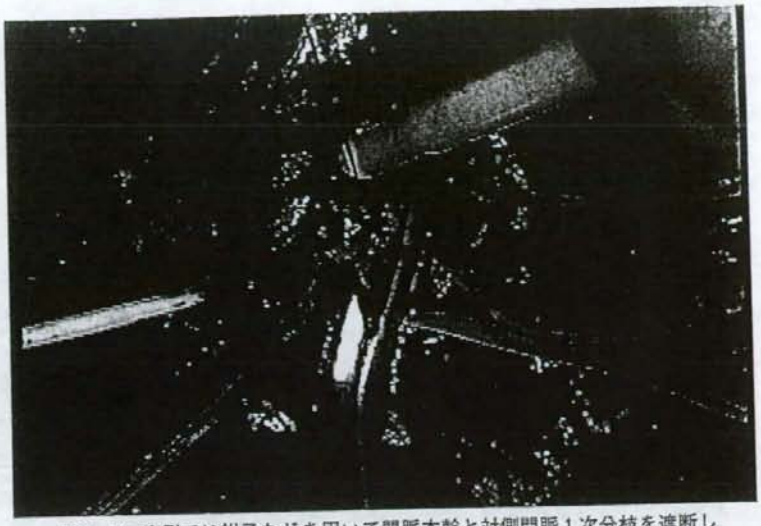

図1　Vp_3症例では鉗子などを用いて門脈本幹と対側門脈1次分枝を遮断した後，腫瘍栓側の門脈1次分枝に支持糸をかけ，メスで切開を加えて，門脈腫瘍栓を摘出する

合，発達した側副血行路や癒痕，胆汁貯留などに注意を要する。

大血管内進展を伴う進行再発肝癌の予後は通常きわめて悪く，下大静脈内腫瘍栓を伴う場合，突然死の危険性がある。そこで，遠隔転移がなく，基本的に全肝内病巣を摘出できる場合で，肝機能が保たれており，全身状態が良好であれば手術適応となる。術後の化学療法の併用を目的とした減量手術も行われる。

大血管内進展を伴った高度進行肝癌に対する手術では，大出血や血流遮断による循環不全や肝障害など過大侵襲が加わる可能性がある。また，術後比較的早期に再発をきたすことが少なくない。そこで，患者および家族には疾患の重症度，手術や再発の危険性とともに術後化学療法を含めた治療プランを十分に説明，理解していただくことが重要である。

門脈腫瘍栓形成例に対する外科的治療

肝内病巣から肝内門脈枝を経て門脈1次分枝(Vp_3)や門脈本幹(Vp_4)に腫瘍栓を形成する。腫瘍栓が対側葉の門脈枝末梢，上腸間膜静脈や脾静脈に及ぶ場合は一般的に切除の適応はない。開腹後，腹腔内精査を行い，次いで術中超音波検査により肝内病巣と門脈腫瘍栓の進展度を把握する。通常，肝門部処理後，門脈腫瘍栓を摘出し，最後に肝切離を行う。すなわち，総胆管をテーピング後，担癌側の肝動脈を結紮・切離する。担癌側の胆管が確認できれば切離しておくと，門脈の全容を確認しやすくなる。門脈本幹のテーピングを行い，左右門脈1次分枝を確保，テーピングする。Vp_4症例では腫瘍栓より尾側まで十分に剝離しておくが，側副血行路が発達している場合が多いため注意を要する。Vp_3症例では鉗子などを用いて門脈本幹と反対側の門脈1次分枝を遮断した後，腫瘍栓側の門脈1次分枝に支持糸をかけ，メスで門脈を切開，門脈腫瘍栓を摘出する（図1）。その後，門脈枝を離断し，断端を縫合閉鎖する。Vp_4症例で腫瘍栓が門脈本幹を占居するような症例では門脈本幹と対側門脈1次分枝を遮断し，門脈本幹に切開を加え，門脈腫瘍栓を摘出する（図2）。時には鈍匙や吸引器を用いて腫瘍栓を摘出する(図3)。さらに門脈本幹の遮断を時々開放して，腫瘍栓を切開口から噴出させる。対側門脈枝に腫瘍栓がみられる場合，Fogartyカテーテルなどを用いて腫瘍栓を摘出する(図4)。その腫瘍栓が摘出されると，対側門脈枝より血液の逆流がみられるようになる。門脈腫瘍栓処理後，肝切除を行うが，尾状葉門脈枝に腫瘍栓がみられる場合は尾状葉合併切除を併施する。

下大静脈内腫瘍栓形成例に対する外科的治療

肝癌の場合，下大静脈内腫瘍栓は直接浸潤によるものはまれで，左・中・右肝静脈，短肝静脈，下右肝静

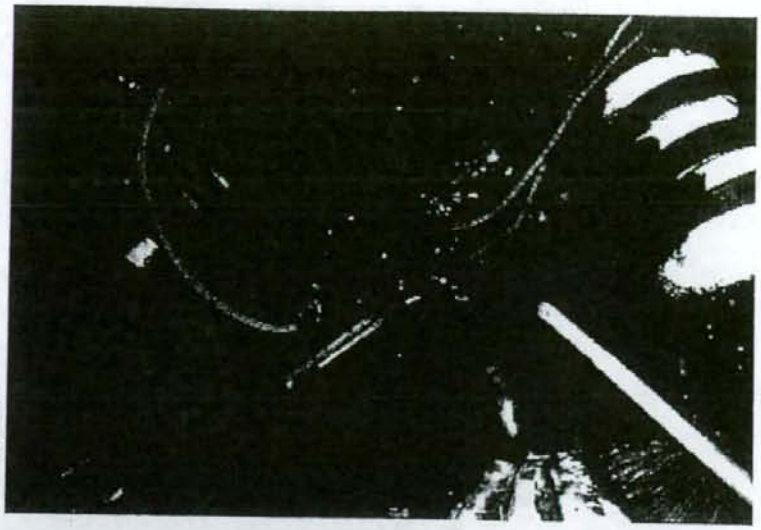

図2　Vp_4症例で腫瘍栓が門脈本幹を占居するような症例では門脈本幹と対側門脈1次分枝を遮断し，門脈本幹に切開を加えて腫瘍栓を摘出する

図3　必要に応じて鉗匙や吸引器を用いて門脈腫瘍栓を摘出する

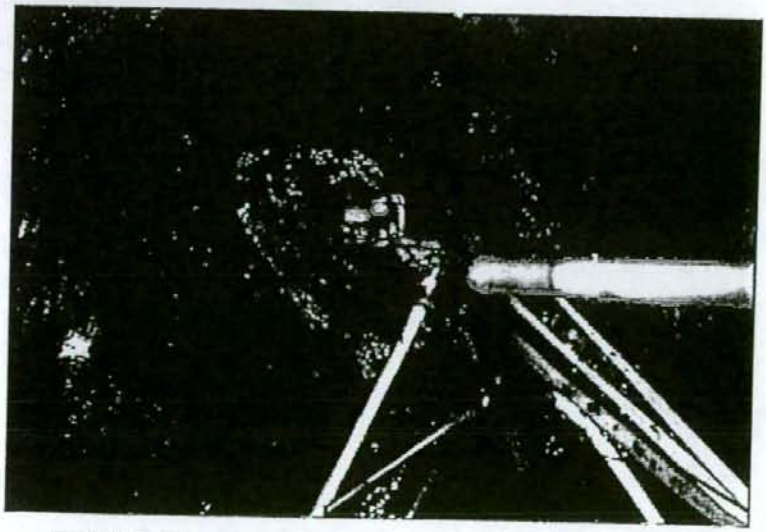

図4　対側門脈枝に腫瘍栓がみられる場合，Fogarty カテーテルなどを用いて腫瘍栓を摘出する

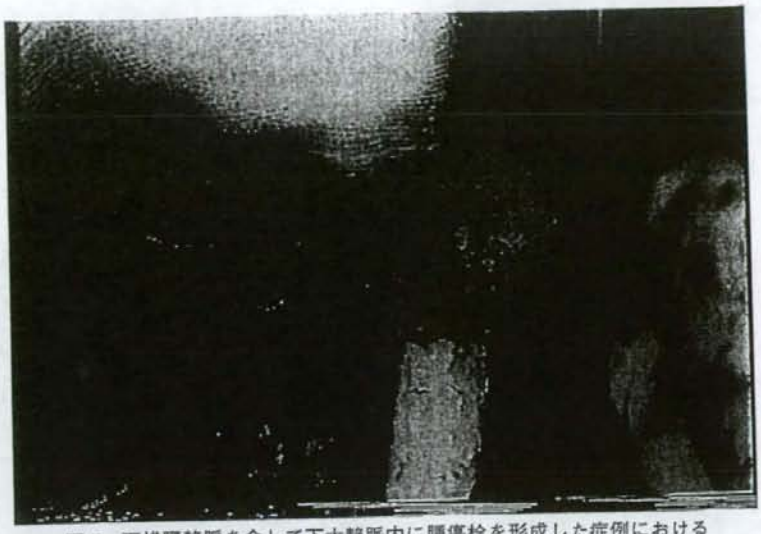

図5　下横隔静脈を介して下大静脈内に腫瘍栓を形成した症例における下大静脈内腫瘍栓摘出

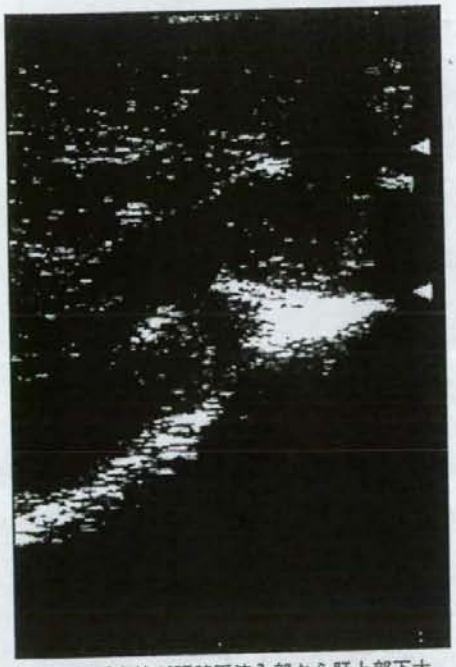

図6　腫瘍栓が肝静脈流入部から肝上部下大静脈内に存在する症例の術中超音波像

脈を介して腫瘍栓が下大静脈内に進展する。筆者らは肝癌の再発病巣から下横隔静脈を介して下大静脈内に腫瘍栓を形成した症例を経験している（図5）。

下大静脈内腫瘍栓を伴う症例に対する手術方法は腫瘍栓の進展部位によって異なる。すなわち，腫瘍栓が右心房内に進展している場合は人工心肺装置が必要となる。肝上部下大静脈内に腫瘍栓が存在し（図6），その頭側にテーピングが可能な場合，全肝血流遮断（total hepatic vascular exclusion：THVE，図7）下に腫瘍栓を摘出し得る。下大静脈腫瘍栓が小さく，肝静脈流入部尾側で下大静脈にテーピングが可能であれば，THVE をせずに摘出が可能である。

THVE を使用する場合，THVE の際のバイパス用に右（左）大伏在静脈，左腋窩静脈を露出できるように術野を設定しておく。開腹後，腹腔内の精査を行い，術中超音波検査によって肝内病巣とともに下大静脈内腫瘍栓の進展度を確認する。腫瘍栓が心房内に達する場合は，経食道超音波検査によって腫瘍栓を確認する（図8）。右心房内に腫瘍栓が進展している場合は，胸骨縦切開を加え，心臓外科の協力の下に人工心肺装置を装着する。この際，肝切離を先行し，人工心肺装着による心停止下に下大静脈から右心房内に進展した腫瘍栓を一塊として切除する方法と，あらかじめ人工心肺下に心停止し，下大静脈から右心房に進展した腫瘍栓を摘出後（図9），肝切離を行う方法が考えられる。

THVE 下に切除可能な場合，Kocher の授動術を行い，腎静脈頭側で下大静脈をテーピングする。次いで，肝上部下大静脈のテーピングを行う。この際，必要があれば下横隔静脈を結紮・切離しておく。横隔膜下でテーピングが困難な場合，経横隔膜的あるいは右開胸を加え，心嚢内でテーピングを行う。経横隔膜的心嚢切開は下大静脈の正中線上で横隔膜に縦切開を加えて

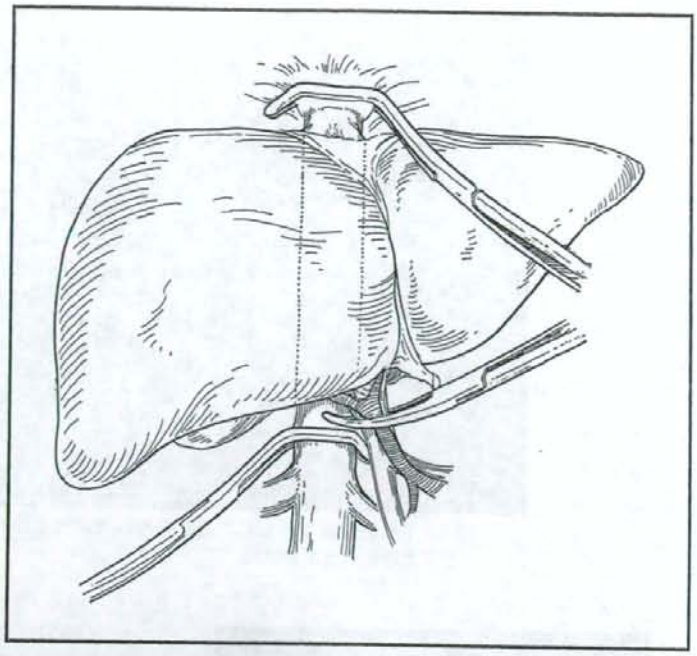

図7　全肝血流遮断（total hepatic vascular exclusion）の模式図

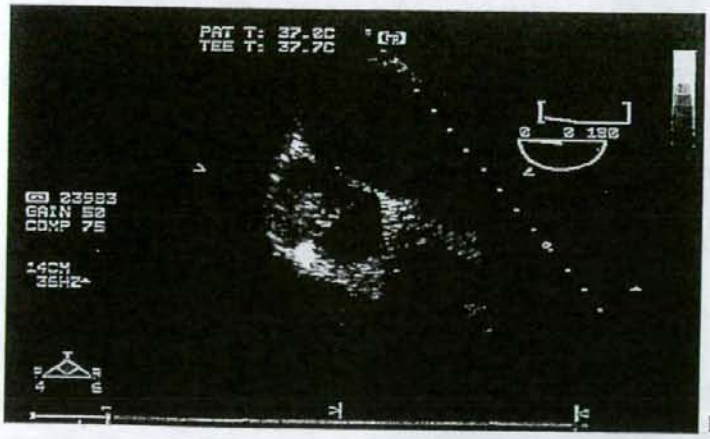

図8　右心房内腫瘍栓の経食道超音波像

図9　人工心肺下，右心房切開による右心房および下大静脈内腫瘍栓の摘出

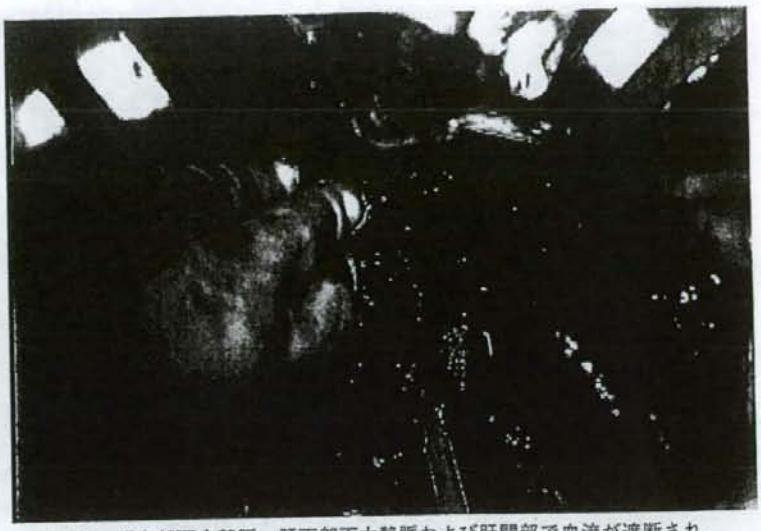

図10　肝上部下大静脈，肝下部下大静脈および肝門部で血流が遮断され，全肝血流遮断が行われている

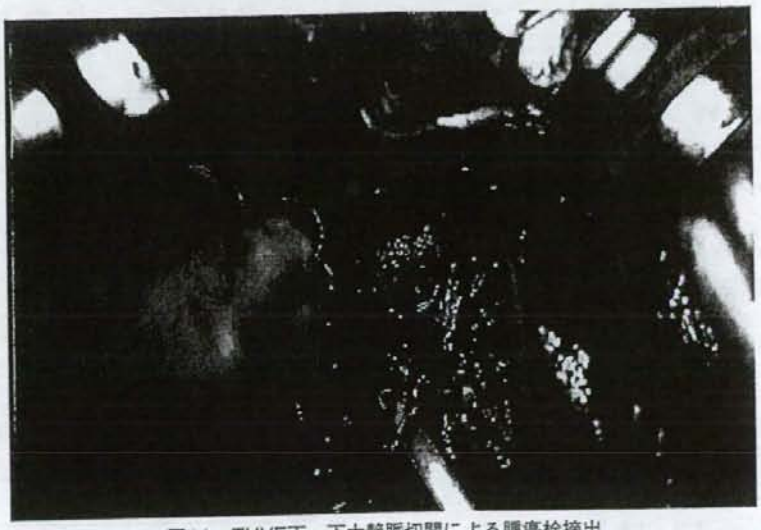

図11　THVE下，下大静脈切開による腫瘍栓摘出

心嚢を開放し，心嚢内肝上部下大静脈をテーピングする。肝門部処理に引き続いて肝を脱転し，下大静脈に流入する短肝静脈を可能なかぎり結紮・切離する。右肝静脈や中・左肝静脈共通幹の下大静脈流入部にテーピングを行うが，腫瘍側の肝静脈の頭側と反対側の肝静脈の尾側に斜めにテーピングしておくことができると，THVEの時間を短縮できる。肝切離を行った後，THVE下に肝静脈や下大静脈を切開し，腫瘍栓を摘出する方法（図10，11）と，THVE下に肝切離および腫瘍栓摘出を行う方法がある。

THVEに際して，まず十分な輸液を行い，中心静脈圧を維持しておく。さらにTHVEに先立ってテストクランプを行う。遮断後5分以内に血圧が低下しなければ基本的にバイパスなしにTHVEは可能である。逆にテストクランプ後，血圧が30％以上低下する場合はバイパスを用意する。正常肝ではバイパスなしで60～90分間のTHVEに耐え得ると報告されている[10]。一方，肝硬変例においてバイパスの設置により

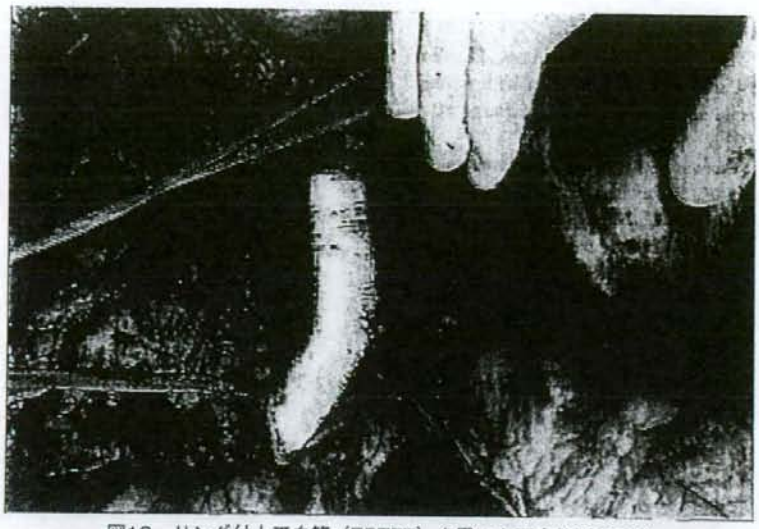

図12　リング付人工血管（EPTFE）を用いた下大静脈の再建

60分間のTHVEが可能と考えられている[9]。バイパスには下大静脈血のみのシングル・バイパスと下大静脈血と門脈血をバイパスするダブル・バイパスがある。血圧維持と腸管のうっ血防止のためにはダブル・バイパスが行われる。また，バイパス方法には血流ポンプを用いるアクティブ・バイパスと血流ポンプを用いないパッシブ・バイパスがあるが，通常ヘパリン化を必要としないバイオポンプを用いたアクティブ・バイパスが選択されることが多い。前述のように，THVE下に腫瘍栓を摘出した後に，肝静脈頭側の肝上部下大静脈で血流遮断している血管鉗子を，健側肝静脈尾側あるいは肝静脈流入部尾側へかけ直すことができれば，全肝の血流遮断を解除することが可能になり肝血流遮断時間を短縮できる。

下大静脈内腫瘍栓が肝静脈流入部付近に存在し，右肝静脈のみで肝右葉が下大静脈と連続している状況であり，肝右葉の尾側への牽引により腫瘍栓が横隔膜より尾側下大静脈内に引っ張れれば，腹腔内操作のみで摘出可能である。さらに肝静脈流入部付近まで移動できれば，下大静脈のサイドクランプのみで摘出可能となる。

肝癌の浸潤により下大静脈合併切除を行う場合，欠損部が小範囲の場合が多く，欠損部が半周程度までであれば直接縫合を行う。欠損部が大きい場合，パッチを用いて縫合閉鎖を行うが，そのパッチには大伏在静脈，下腸間膜静脈，卵巣（精巣）静脈，心膜，人工血管などを用いる。下大静脈を再建する場合，径2cmのリング付人工血管（EPTFE）を用いて再建する（図12）。

大血管内進展を伴う進行再発肝癌の併用療法

筆者らはVp3あるいはVp4症例に対しては切除後にlow dose FP療法を中心とした肝動注療法を施行し，再発予防に努めている。また，高度進行肝癌に対する減量手術後の化学療法施行例の成績も報告され，長期生存例もみられるようになった[4~6]。今後，これらの総合的な治療戦略の確立により，大血管内進展を伴う進行再発肝癌の治療成績の向上が期待される。

おわりに

大血管内進展を伴う進行再発肝癌に対する手術は，術中大出血をきたす可能性や全身循環や肝障害がみられるなど侵襲がきわめて大きい治療であるので，慎重な手術適応決定と心臓外科などとの協力体制が重要である。

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1．B 型肝炎と肝細胞癌

Hepatitis B virus and hepatocellular carcinoma

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