were analyzed in the 50 patients with MCHM (Table 2). Maximum tumour size above 5 cm ($P = 0.02$), CEA level before hepatectomy above 20 ng/ml ($P = 0.01$), tumour volume ratio above 8% ($P = 0.04$), and CV in tumour volume above 1.8 ($P < 0.01$) were significantly associated with poor overall survival.

We examined the independent predictive value of the aforementioned factors in overall survival. The data were analyzed using a Cox regression model (Table 3). Maximum size of the tumour was excluded from the analysis because it was strongly correlated with tumour volume. Then, only CV in tumour volume above 1.8 ($P = 0.01$; HR = 4.08; 95% CI, 1.33 to 12.5) had predictive value for decreased overall survival after resection of MCHM. Fig. 2 shows a case of MCHM with low CV (a) and another one with high CV (b) in tumour volume. The median survival of patients with CV in tumour volume below 1.8 was 25.0 months and that above 1.8 was 16.1 months (Fig. 3).

Table 2
Correlation between clinicopathological factors and overall survival after hepatectomy for multiple colorectal hepatic metastases

	No. of patients	Median survival (mo)	P
Primary colorectal lesion			
Location			
Colon	31	23.4	0.63
Rectum	19	18.5	
Stage (TNM classification)			
I, II	10	20.4	0.44
III, IV	40	22.7	
Lymph node metastasis			
Absent	18	23.4	0.82
Present	32	19.7	
Histological type of adenocarcinoma			
Well or moderately differentiated	46	23.5	0.08
Poorly differentiated and others	4	12.5	
Hepatic metastases			
Number of tumours			
<5	20	21.1	0.61
≥5	30	23.4	
Maximum size of the tumour (cm)			
<5	40	23.5	0.02
≥5	10	15.9	
Distribution of metastases			
Unilobar	12	21.1	0.60
Bilobar	38	23.4	
Microscopic surgical margin			
Negative	39	23.4	0.95
Positive	11	21.3	
CEA level before treatment (ng/ml)			
<20	27	24.6	0.01
≥20	23	17.5	
Tumour volume ratio* (%)			
<8	41	23.4	0.04
≥8	9	17.5	
Coefficient of variation† in tumour volume			
<1.8	42	25.0	<0.01
≥1.8	8	16.1	
Synchronous/Metachronous			
Synchronous	24	24.4	0.80
Metachronous	26	18.0	
Interval between colorectal resection and hepatectomy			
<1 year	39	24.6	0.91
≥1 year	11	12.1	
Adjuvant chemotherapy after hepatectomy			
Absent	41	23.5	0.61
Present	9	16.4	

CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Table 3
Multivariate analyses of factors affecting overall survival after hepatectomy for multiple colorectal hepatic metastases

	Hazard Ratio (95% C.I.)	P
Hepatic metastases		
CEA level before treatment (ng/ml)		
<20	reference	0.07
≥20	2.39 (0.93–6.16)	
Tumour volume ratio* (%)		
<8	reference	0.87
≥8	1.10 (0.36–3.39)	
Coefficient of variation† in tumour volume		
<1.8	reference	0.01
≥1.8	4.08 (1.33–12.5)	

C.I., confidence interval; CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Discussion

Several reports have described the efficacy of resection for MCHM. Bolton et al. analyzed clinical outcomes of 165 patients who underwent hepatic resection for colorectal metastases, and evaluated its efficacy and safety for patients with more than four and/or bilobar hepatic metastases.[6] The prognosis for such patients was almost equal to that of patients with fewer than four and unilobar hepatic metastases. Weber et al. reported that the 5-year survival rate after hepatic resection for 155 patients with four or more metastases was 23%, and twelve 5-year survivors were observed.[19] Minagawa et al. similarly reported a 32% 5-year survival of patients with four or more tumours.[13] In the present study, overall survival after hepatic resection for MCHM was 48% at 3 years and 43% at 5 years. Our results reconfirm that hepatic resection is beneficial for some patients with MCHM of colorectal cancer.

We found that a CV in tumour volume of above 1.8 was the only independent poor prognostic factor after resection of MCHM. Dispersion of tumour volume for each tumour is variable among patients. However, no previous study has attempted to quantify the dispersion of tumour volume or to evaluate its prognostic significance in colorectal hepatic metastases, and then we studied the association between the dispersion of tumour volume, quantified by CV, and survival after hepatectomy. Coefficient of variation is a statistical measure of the dispersion of data. It represents the ratio of the standard deviation to the mean, and is a useful statistic for comparing the degree of deviation from one

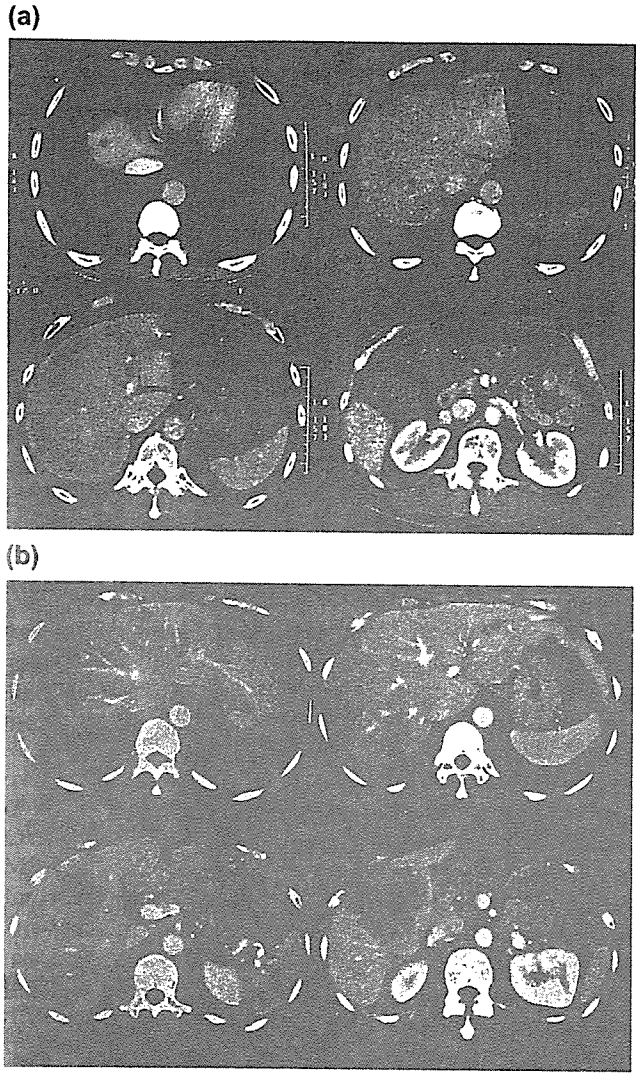

Figure 2. (a) A case of MCHM with low CV (=0.41) in tumour volume. (b) A case of MCHM with high CV (=3.20) in tumour volume.

data series to another, even if the means are drastically different from each other.[20,21] The mean tumour size varied widely among patients and CV was more useful than standard deviation in the present analyses.

The reason why high CV in tumour volume is strongly associated with independent poor prognosis after hepatic resection is obscure. However, a high CV may denote the coexistence of huge and tiny tumours. We propose two hypotheses to explain the association between high CV and poor prognosis. The first is that a high CV means the existence of a rapidly growing tumour; the high CV may result from the coexistence of tiny tumours growing at an ordinary rate and a huge tumour with an extremely aggressive nature and rapid growth. Another hypothesis is that high CV means a huge tumour with many intrahepatic metastases. Tiny tumours might have metastasized, not from the primary colorectal tumour, but from this huge hepatic tumour. Accordingly, a high CV might reflect progressive characteristics of MCHM.

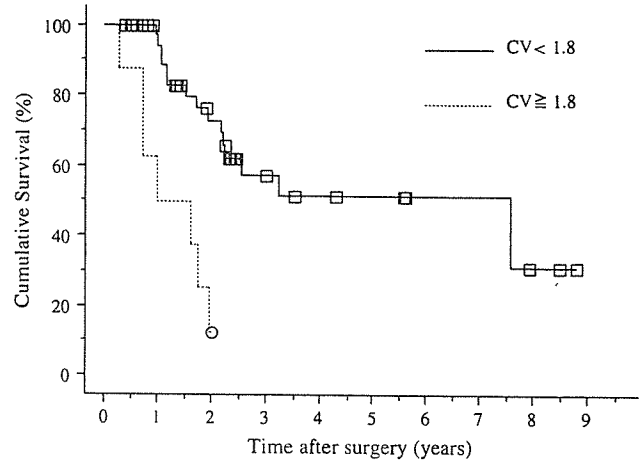

Figure 3. Cumulative survival curves after hepatic resection of MCHM according to CV in tumour volume. The median survival of patients with CV in tumour volume below 1.8 was 25.0 months and that above 1.8 was 16.1 months. Survival of patients with CV in tumour volume above 1.8 was poorer than that of patients with CV in tumour volume below 1.8 ($P < 0.01$).

In 8 patients with CV > 1.8, 6 suffered from severe hepatic recurrence after hepatic resection. In the remaining 2 patients, although lymph node recurrence was initially observed, hepatic recurrence with much tumour burden was recognized in the next few months. Then, severe hepatic recurrence could be a characteristic pattern of recurrence in patients with CV > 1.8. High CV might suggest extensive micro-metastases in the remnant liver.

Node-positive primary tumour,[4,22,23] serosal involvement of primary tumour,[22,23] stage of the primary tumour,[8,13] histological differentiation of primary tumour[22], a short disease-free interval from the primary tumour to metastasis,[4,11] extrahepatic disease at hepatectomy,[3,4,11,22,23] high CEA levels before hepatectomy,[4,5,8,10,22] large size of hepatic tumour,[4,8,23] the number of hepatic tumours,[4,5,8–13,22,23] bilobar distribution of hepatic tumour,[11] lymph node metastasis during hepatectomy,[3,11,13] an advanced age at hepatectomy,[8] and a positive margin of hepatectomy[4,5,8–11,22] have been reported as poor prognostic factors after resection of MCHM. However, the factors mentioned above were not found to be prognostic factors in this study. The difference between our results and those of other studies was partly due to difference of population. Patients of the present study consisted of only those with four or more metastatic lesions of colorectal cancer in the liver. Moreover, the difference might have resulted from the fact that CV in tumour volume, which had not been evaluated as a prognostic factor in other studies, affected patients' survival much more strongly than the aforementioned factors did in the present study.

In our study, the median survival of patients with CV in tumour volume above 1.8 was only 16 months and no 2-year survivors were found. Results of the present study lead us to conclude that hepatic resection is not

recommended as an initial treatment for MCHM when CV in tumour volume is above 1.8. Those patients should be treated by systemic chemotherapy and surgical resection then should be considered when the disease responds to the therapy.

Selecting the appropriate strategy according to the tumour staging has been an issue for patients with MCHM. Several studies proposed clinical risk scores incorporating the prognostic factors for predicting recurrence or prognosis after resection of MCHM to answer the clinical question.[4,8,11,23,24] However, those scoring systems and the factors consisting of each scoring system are not identical among the studies. The standard algorithm of treatment for MCHM is still obscure. Definitive and universal factors or a scoring system for predicting recurrence and prognosis after resection of MCHM is needed, and CV might be one of those factors in cases of MCHM.

The multistep process involving mutational events on both oncogenes and tumour suppressor genes is accepted for development of colorectal cancer, and several studies have shown that allelic imbalance correlated with staging and prognosis in colorectal cancer.[25,26] High CV might be caused by some genetic alterations. Genetic analysis such as evaluations of difference between the allelic imbalance of small tumours and that of large tumours in patients with high CV or evaluations of difference between the allelic imbalance of tumours in patients with low CV and that of tumours in patients with high CV may indicate particularly sensitive genomic regions and offer new information about the development of colorectal cancer. Further study is warranted to verify the prognostic significance of CV in tumour volume.

In conclusion, hepatic resections for MCHM sometimes contribute to long-term survival. Coefficient of variation in tumour volume above 1.8 might predict poor survival after hepatectomy of MCHM and be useful in planning the therapeutic strategy for patients with MCHM.

Acknowledgement

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Positron Emission Tomography with F-18 Fluorodeoxyglucose in Evaluating Colorectal Hepatic Metastasis Down-staged by Chemotherapy

SHINICHIRO TAKAHASHI[1], YOSHIHUMI KUROKI[2], KATSUHIRO NASU[2], SHIGERU NAWANO[2], MASARU KONISHI[1], TOSHIO NAKAGOHRI[1], NAOTO GOTOHDA[1], NORIO SAITO[3] and TAIRA KINOSHITA[1]

[1]Department of Hepato-biliary Pancreatic Surgery, [2]Department of Diagnostic Radiology and [3]Department of Colorectal Surgery, National Cancer Center Hospital East, Chiba, Japan

Abstract. *Background: The efficacy of positron emission tomography with ^{18}F fluoro-2-deoxy-D-glucose (FDG-PET) is obscure in evaluating viability or the extent of colorectal hepatic metastasis (CHM), down-staged by chemotherapy. Patients and Methods: A retrospective lesion-by-lesion analysis was performed for seven consecutive patients, who had received rescue hepatectomy for initially unresectable CHM, in order to evaluate the correlation between results of imaging modalities and the corresponding pathology. Results: The sensitivity and positive predictive value of the conventional modalities (CT and MRI) were 92% and 42%, respectively, while the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were 58%, 100%, 100% and 75% respectively. The sensitivity of FDG-PET was 100% in evaluating the viability of tumors >2 cm, however, this fell to 17% in tumors <2 cm. Conclusion: FDG-PET is effective in assessing the viability of tumors >2 cm, but not those <2 cm, in patients with CHM down-staged by chemotherapy.*

Unresectable hepatic metastasis is one of the major obstacles in the treatment of colorectal cancer. Systemic chemotherapy for unresectable colorectal cancer has improved recently with the introduction of new effective agents (1-4). Even so, chemotherapy is rarely curative. Rescue hepatectomy after down-staging by chemotherapy is a potential treatment for unresectable colorectal hepatic metastasis (CHM) (5-8). However, pre-operative evaluation of tumor extent or viability is one of the issues in this strategy. The indication for rescue hepatectomy is based on the interpretation of the imaging of tumor extent or viability after down-staging by chemotherapy, however, evaluating the viability of hepatic tumors treated with chemotherapy is sometimes difficult by conventional imaging methods, such as computed tomography (CT) or magnetic resonance imaging (MRI), especially when the tumors have shrunk remarkably or exhibit notable calcification, after chemotherapy. Therefore, an effective diagnostic imaging modality to evaluate the viability of hepatic tumors after chemotherapy is needed.

Positron emission tomography with ^{18}F fluoro-2-deoxy-D-glucose (FDG-PET) is a functional imaging technique based on the increased utilization of glucose by tumor cells, and is effective for staging colorectal cancer (9, 10). Furthermore, the ability of FDG-PET to assess the pathological response to chemotherapy has been suggested in various malignant tumors (11-15). The correlation in CHM between FDG-PET findings and those of corresponding pathology has not been fully examined.

The present study was conducted to examine whether FDG-PET was able to assess tumor viability, before rescue surgery, for initially unresectable CHMs down-staged by chemotherapy and indicate which tumors should be resected.

Patients and Methods

Patient population. Seventy-four patients underwent hepatic resection for CHM at the National Cancer Center Hospital East, Japan, between January 2004 and July 2005, and 10 out of these underwent hepatic resection, after down-staging by chemotherapy. Since January 2004, all patients about to undergo rescue surgery are examined using FDG-PET pre-operatively, when informed consent is granted. Consequently, seven consecutive patients, who had been examined by CT, MRI and FDG-PET, were included in the present study. The patients were four men and three women, ranging from 44 to 70 years old. The location of the primary colorectal tumor was the colon in five patients and the rectum in two patients. All the

Correspondence to: Shinichiro Takahashi, MD, Department of Hepato-biliary Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Chiba, Japan. Tel: +81-471-33-1111, Fax: +81-471-31-4724, e-mail: shtakaha@east.ncc.go.jp

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primary tumors were well- or moderately-differentiated adenocarcinomas. The primary tumors were staged as II (n=2), III (n=2), and IV (n=3) according to the TNM classification.

Chemotherapy. The reasons for choosing chemotherapy instead of curative resection, initially, were multiple bilobar tumors in five patients, invasion to the bilateral bile ducts and portal veins in one and invasion to the 3 major hepatic veins in one. The chemotherapies performed for the unresectable tumors were 5-fluorouracil-leucovorin combined with irinotecan in four patients, 5-fluorouracil-leucovorin alone in one, oral uracil/tegafur in one and capecitabine in one. Five patients experienced a partial response and two patients had stable disease, based on the Response Evaluation Criteria in Solid Tumors.

Conventional imaging (CT, MRI). All patients underwent contrast-enhanced CT and MRI before hepatectomy. Multi slice CT with 16 DAS was used for this study (Aquillion, Toshiba Medical Sysytems, Japan). CT images were obtained using 5 mm collimation after administration of 100 ml of nonionic iodine intravenous contrast medium injected at 3 ml/sec with a 70-sec delay (portal-dominant phase). Images were reconstructed at 5 mm intervals using a standard soft-tissue algorithm.

MR images were aquired using a 1.5-T MR imager (Gyroscan Intera, Philips Medical Systems, Netherlands) with a phased array coil. A section thickness of 7 mm with a 1 mm gap was used for all sequences. T1-weighted fast field-echo image, T2-weighted fast spin-echo image and diffusion-weighted image with b factor 500 sec/mm^2 were performed. After gadodiamide injection, T1-weighted fast field-echo dynamic image were also obtained during the hepatic arterial, portal venous and delayed phases.

FDG-PET. Whole body FDG-PET was performed in five patients using a GE Advance Scanner (General Electric Medical System, Milwaukee, WI, USA), which has an axial field of view of 15 cm and a spatial resolution of 4.5 mm full-width-half-maximum. All patients fasted for at least 4 h prior to scanning. Sixty min after intravenous injection of 300 MBq of F18-FDG, emission scanning was performed in 5 min and transmission scanning in 1 min. Data acquisition was performed in 7 bed positions.

In the remaining two patients, PET/CT scanning was performed using a Discovery LS PET/CT system (General Electric Medical Systems, Waukesha, WI, USA) because our PET system had been replaced by PET/CT. The CT component was performed using a multi-detector scanner. The parameters were 140 kV, 80 Ma, 0.8 s/CT rotation, a pitch of 6, and a table speed of 22.5 mm/s. Scans were acquired from the skull base to mid-thigh level, in 7 bed positions, with a total acquisition time of 31.9 sec to 37 sec. CT data was resized from a 512x512 matrix to a 128x128 matrix to match the PET data, to allow for image fusion and generation of CT transmission maps. The PET data were also acquired in the same anatomic positions; in 7 bed positions at 5 min per position.

All PET studies were performed at least 4 weeks after completion of chemotherapy.

Rescue hepatectomy. At the National Cancer Center Hospital East, Japan, all lesions considered positive for malignancy, by any pre-operative diagnostic imaging evaluation, were resected by rescue hepatectomy. During this operation, all the tiny suspicious lesions that were definitive metastases before chemotherapy were resected.

In our patients, a careful search was performed after laparotomy for local recurrence, extrahepatic metastases and peritoneal dissemination in the abdominal cavity. Any suspicious lesions were examined by biopsy. Intra-operative bimanual liver palpation and ultrasonography were performed to confirm tumor location and size, in all seven patients and all of the resections were ultrasound-guided procedures. Hepatic resection was performed with tumor-free resection margins, by the forceps fracture method, under inflow occlusion (Pringle's maneuver). When small lesions that had been detected by pre-operative imaging could not be recognized by either palpation or intra-operative ultrasonography, the estimated part or segment of the liver occupied by the lesions was resected.

Extended lobectomy and multiple partial resections were performed on two patients each, and central bi-segmentectomy, lobectomy, and segmentectomy were performed on one patient each, according to Couinaud's anatomical classification.

Assessment of tumor viability with FDG-PET. In our hospital, when interpreting conventional CT and MRI findings, any hepatic lesions are classified according to the degree of confidence that a metastatic tumor is present, as follows: definitely present, probably present, possibly present, probably absent and definitely absent. Lesions that fall into the definitely present, probably present and possibly present categories are considered positive for malignancy, while lesions that fall into the other categories are considered negative. Lesions which are positive, by either CT or MRI, are considered positive by conventional examination.

In the present study, the category "possibly present" included the small lesions, detected using conventional imaging, that were used to indicate definitive metastasis, but which then could not be determined as viable or otherwise, due to a reduction in size or remarkable calcification after chemotherapy (Figure 1).

All lesions considered positive by conventional examination were compared with their corresponding pathology findings, as the standard reference and the sensitivity and positive predictive value were then calculated. Furthermore, these lesions were also assessed by FDG-PET according to the degree of confidence of malignancy, *i.e.* definitely present, probably present, possibly present, probably absent, and definitely absent. A discrete focus with increased FDG accumulation, markedly greater than that in the hepatic parenchyma, was interpreted as malignancy, being definitely present or probably present. Focally increased FDG uptake, minimally greater than in the liver, was considered possibly positive for malignancy, but heterogeneous uptake in the hepatic parenchyma without a focal lesion was considered to indicate that malignancy was probably absent. Lesions in the definitely present, probably present and possibly present categories were considered positive for malignancy, while those in the probably absent and definitely absent categories were considered negative.

FDG-PET findings were also compared with the pathology findings, as the reference, and then sensitivity, specificity, positive predictive value and negative predictive value were calculated according to tumor size: <2 cm and >2 cm.

Finally, the sensitivities, specificities, positive predictive values and negative predictive values were compared between the subgroups according to tumor size. The results of each imaging test were interpreted by at least two experienced radiologists.

Pathological examination. The resected hepatic specimens were fixed in 10% phosphate-buffered formalin, sliced at 5 mm intervals and embedded in paraffin. The findings of all lesions, considered positive

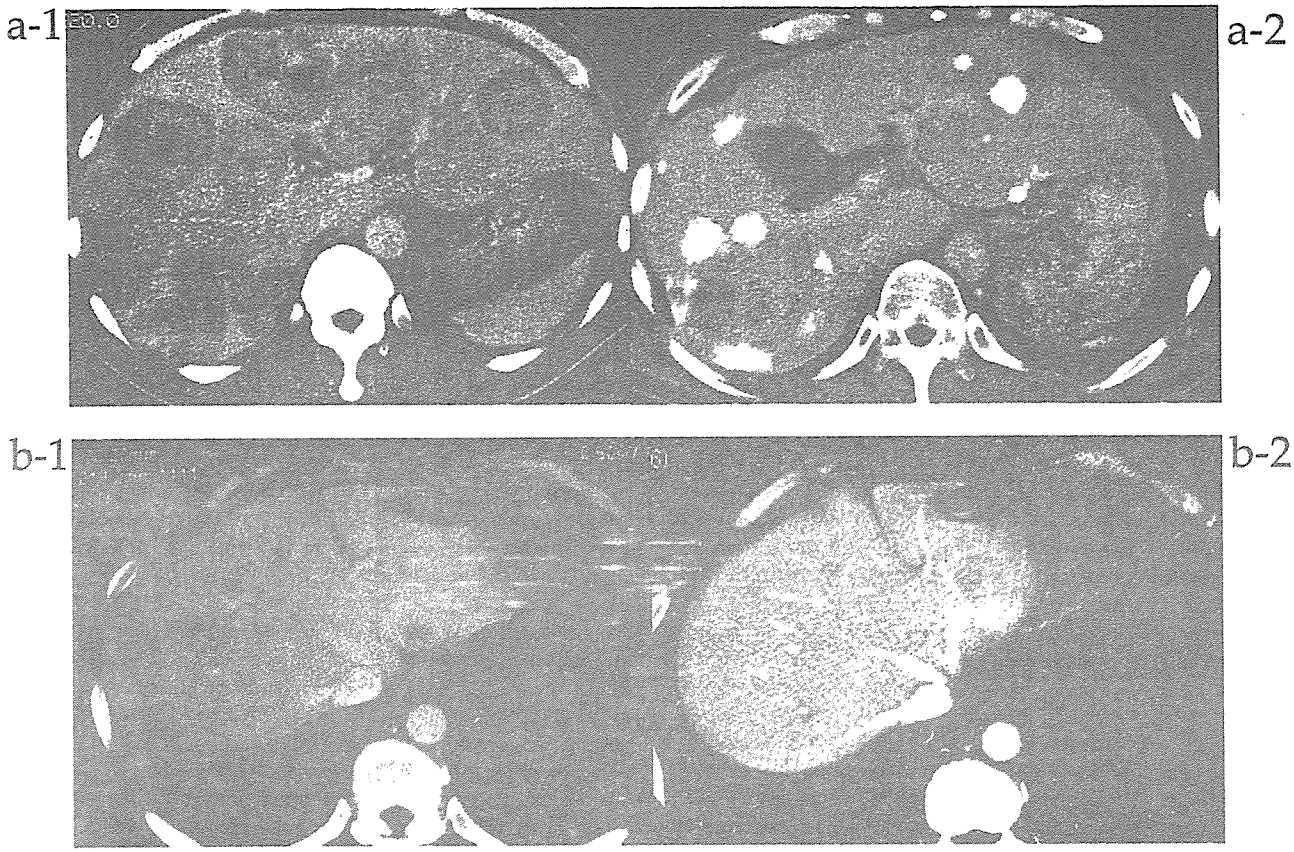

Figure 1. *a) A 45-year-old male with initially unresectable multiple colorectal hepatic metastases. (a-1) CT before chemotherapy. (a-2) CT after chemotherapy. Significant calcification was seen in the tumors. After rescue hepatectomy, histological examination revealed adenocarcinoma in most of the calcificated tumors. b) A 65-year-old female with multiple colorectal hepatic metastases. (b-1) CT before chemotherapy. (b-2) CT after chemotherapy. Tumors had reduced markedly in size.*

by any diagnostic imaging or intra-operative examination, were confirmed macroscopically and the lesions were then examined microscopically to evaluate viability. Serial sections 3 μm thick were stained with hematoxylin and eosin (H&E) for morphological examination. Histological diagnoses were based on the World Health Organization classification (16).

Statistical analysis. χ^2 analysis was used to assess sensitivity, specificity, positive predictive value and negative predictive value between subgroups according to tumor size. A p-value of less than 0.05 was considered to denote statistical significance.

Results

In the seven patients with CHMs down-staged by chemotherapy, 27 lesions were resected, all of which were considered positive for malignancy by pre-operative diagnostic imaging or intra-operative examination. Among the 27 lesions, 26 were deemed positive by at least one imaging modality, while the other could not be evaluated using imaging and was diagnosed by intra-operative examination. Twelve lesions were histologically diagnosed as adenocarcinoma, but no malignancies were demonstrated in the remaining 15 lesions.

CT and MRI led to 26 lesions being diagnosed as malignant, while only 7 of these 26 lesions were considered positive by FDG-PET (Figure 2). No lesion was positive only by FDG-PET.

Table I. *Comparisons of interpretations of CT, MR images and FDG-PET with pathology.*

	Pathological findings	
Imaging finding	Malignancy (12)	No malignancy (15)
CT and MR Imaging		
Positive (26)	11	15
Negative (1)	1	0
FDG-PET		
Positive (7)	7	0
Negative (20)	5	15

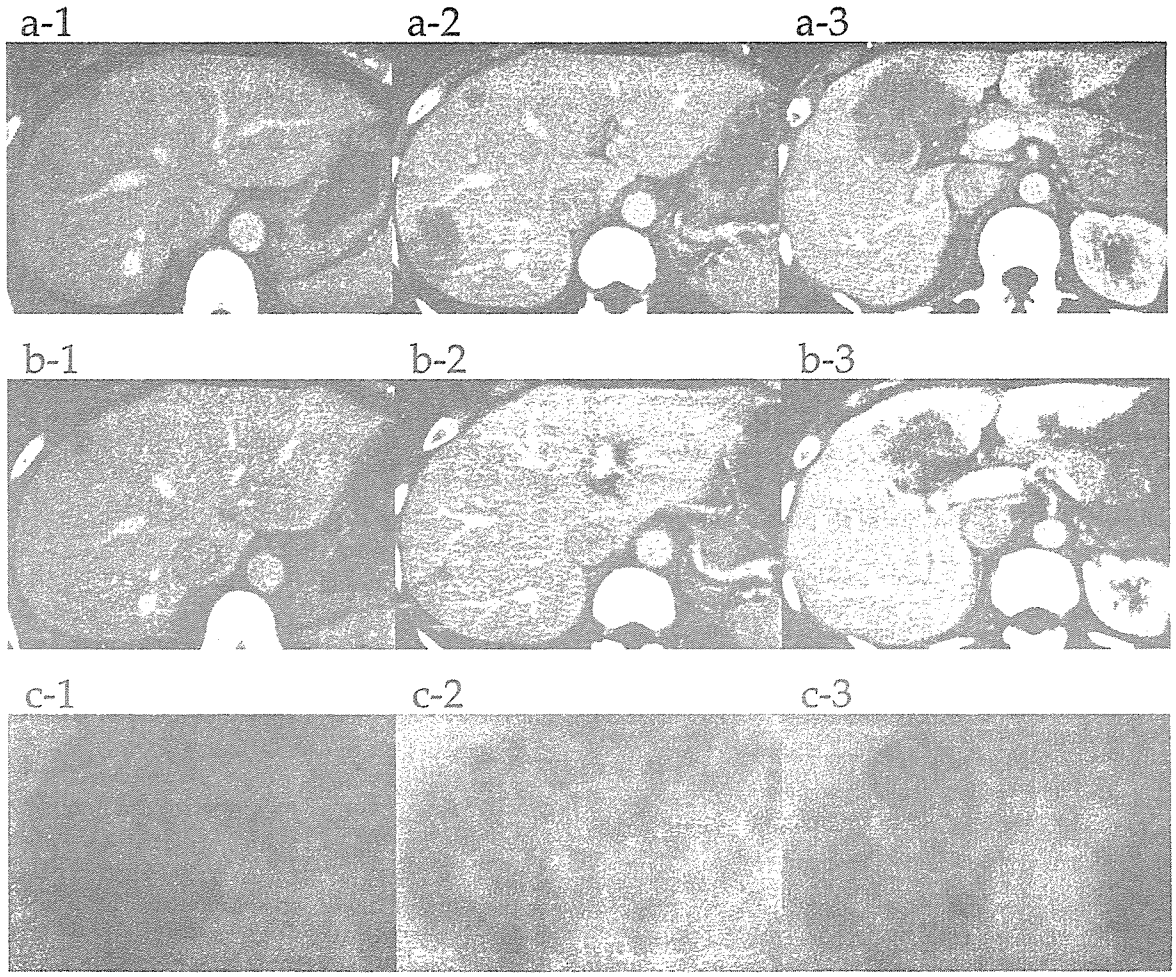

Figure 2. *A 44-year-old female with multiple colorectal hepatic metastases. (a-1, 2 and 3) CT before chemotherapy. Tumors were initially unresectable because of invasion to the hepatic hilum. (b-1, 2 and 3) CT after chemotherapy. Tumors in segments III, IV / V and VII showed significant reduction in size. (c-1, 2 and 3) FDG-PET after chemotherapy. By FDG-PET, tumors located in segments IV / V and VIII were considered positive, but tumors in segments III and VII were negative. Extended left lobectomy plus partial resections were performed. Tumors in segments III, IV / V and VIII proved histologically to be adenocarcinoma, but the tumor in segment VII had no viable cells.*

The interpretations of the conventional (CT/MRI) findings and FDG-PET findings were compared with the results of pathology in Table I. The sensitivity and positive predictive value of the conventional modalities were 92% (95% *CI*=0.73-1.00) and 42% (0.22-0.63), respectively, while the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were 58% (95% *CI*=0.26-0.91), 100% (1.00-1.00), 100% (1.00-1.00) and 75% (0.54-0.96), respectively.

An assessment of the accuracy of conventional imaging and FDG-PET, according to tumor size (Table II), revealed that interpretation of the conventional findings and FDG-PET was highly accurate in lesions >2 cm. However, in lesions <2 cm, the positive predictive value for conventional imaging was only 26%, while the sensitivity for FDG-PET was only 17%, both of which were significantly lower than in lesions >2 cm. The specificity and negative predictive value of conventional imaging were not calculated, because lesions negative by both CT and MRI, were not resected, except for one which was diagnosed as positive by intra-operative examination. The viability of the 27 tumors could not be determined by any cut-off value of tumor-size (data not shown).

Discussion

We assessed the efficacy of FDG-PET in evaluating the tumor viability of CHM down-staged by chemotherapy, before rescue surgery. Our results indicate that FDG-PET is only effective in assessing the viability of hepatic lesions >2 cm after chemotherapy.

Table II. *Accuracies of CT, MRI, and FDG-PET in evaluation of tumor viability according to tumor size.*

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	*P*-value
CT, MRI tumor size					
<2 cm	83 (5/6; 0.41, 1.00)	–	26 (5/19; 0.05, 0.48)*	–	<0.01*
≥2 cm	100 (6/6; 1.00, 1.00)	–	86 (6/7; 0.51, 1.00)*	–	
FDG-PET tumor size					
< 2 cm	17 (1/6; 0.00, 0.60)†	100 (14/14; 1.00, 1.00)	100 (1/1; –, –)	74 (14/19; 0.52, 0.96)	<0.01†
≥2 cm	100 (6/6; 1.00, 1.00)†	100 (1/1; 1.00, 1.00)	100 (6/6; 1.00, 1.00)	100 (1/1; –, –)	

Numbers in parentheses are the data used to determine the percentages and the 95% confidence intervals. *Difference between positive predictive value of CT and MRI in tumor <2 cm and that in tumor ≥2 cm. †Difference between sensitivity of FDG-PET in tumor <2 cm and that in tumor ≥2 cm.

The ability to use FDG-PET to assess the pathological tumor response to pre-operative chemotherapy, radiation or other treatment has been suggested in several tumors (11-15). In addition, correlation between decreased uptake in FDG-PET and histopathological response in the resected specimen was observed in patients, who underwent pre-operative chemotherapy or chemoradiotherapy for esophageal squamous cell carcinoma (17, 18), rectal cancer (19) and gastric carcinoma (20). However, the correlation between uptake in FDG-PET and the corresponding pathological findings has not been studied fully in CHM.

In the present study, portal phase helical CT and MRI were used as the conventional modalities. In our institution, diagnosis based on either, is routinely performed before hepatic resection for CHM, because portal phase helical CT has shown excellent sensitivity in detecting CHM and is considered as the standard pre-operative examination for CHM (21-23). Furthermore, SPIO-enhanced MRI and diffusion-weighted sensitivity encoding MRI have demonstrated high sensitivity equal to that of portal phase helical CT, and have excellent specificity in detecting CHM (24-26).

The present lesion-by-lesion analysis demonstrated that only 11 out of the 26 lesions that had pathological malignancy, considered positive for malignancy by conventional imaging. In the conventional examinations, the sensitivity of 92% for detecting hepatic viable CHMs was similar to that in the aforementioned studies, but the positive predictive value in tumors <2 cm was only 26%. Thus, CT and MRI were able to detect even small tumors, but could hardly evaluate the viability of small tumors after down-staging by chemotherapy.

On the other hand, FDG-PET showed excellent specificity (100%) and positive predictive value (100%), irrespective of tumor size. In tumors >2 cm, the sensitivity and negative predictive value for FDG-PET were both 100%. However, in tumors <2 cm, sensitivity was extremely low (17%). Thus, many of the tumors that shrunk to <2 cm by chemotherapy were undetectable by FDG-PET.

The reasons for this low sensitivity of FDG-PET in tumors <2 cm may be low spatial resolution, the partial volume effect and decreased FDG uptake in tumor tissue, after chemotherapy. Several groups reported that the sensitivity of FDG-PET for CHM was related to tumor size (27, 28). Lower sensitivity to smaller tumors was shown to be caused by the relatively low spatial resolution of FDG-PET and decreased measured activity concentration owing to the partial volume effect (29, 30). The partial volume effect reduces the measured activity concentration to a greater extent in smaller tumors.

Low sensitivity in FDG-PET has also been ascribed to the effects of chemotherapy itself. Chemotherapy may alter FDG uptake in two ways. First, the chemotherapy may reduce FDG uptake, by causing functional changes in tumor glucose metabolism. Spaepen *et al.* demonstrated that changes in tumor glucose metabolism occured rapidly after chemotherapy, as demonstrated using transplants of Daudi cells in SCID mice (31). Second, a decrease in viable cells by necrosis or apoptosis induced by chemotherapy may diminish FDG uptake in the tumor. Swisher *et al.* studied the correlation between the percentage of residual tumor and standardized uptake value (SUV) of FDG-PET after pre-operative chemoradiation in patients with esophageal cancer (18). They found that patients with >50% histological tumor viability had a significantly higher average SUV compared with those with <50% histological tumor viability. However, the SUV of tumors with no viability was similar to that of tumors with 10-50% tumor viability. Accordingly, when chemotherapy shows excellent efficacy in CHMs, it is extremely difficult to detect the resulting low FDG uptake by PET.

Our results suggest that the viability of small tumors that have been down-staged by chemotherapy can hardly be evaluated by CT, MRI or FDG-PET. Thus, at the moment, lesions considered positive by either CT or MRI should be treated by surgical resection in order to avoid leaving viable metastases in the residual liver. When surgical resection is not suitable for the specific lesion, perhaps due the small amount of residual liver, locoregional therapy, such as radiofrequency ablation or cryosurgery may become the preferred treatment options (6, 7).

The present study has nevertheless some limitations. The number of subjects in our study was relatively small, although the results have significant implications for rescue surgery for CHMs after chemotherapy. Furthermore, only two of the seven patients underwent PET/CT. The recent introduction of combined FDG-PET and CT has improved imaging accuracy by allowing accurate anatomical localization of FDG uptake. The sensitivity of PET/CT may be superior to that of FDG-PET for the detection of viable CHMs after chemotherapy. However, a major improvement in sensitivity is not expected, because the fundamental problem of detecting small viable tumors in PET is not resolved even using PET/CT.

New functional imaging with higher sensitivity for detecting small viable tumors is necessary to improve rescue surgery for CHM.

FDG-PET can be used to accurately assess the viability of CHMs >2 cm, before rescue surgery for initially unresectable CHMs down-staged by chemotherapy, but cannot be used for hepatic tumors <2 cm, because of the extremely low sensitivity of FDG-PET for such tumors.

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The Role of a Protease Inhibitor against Hepatectomy

Naoto Gotohda[1], Hiromi Iwagaki[2], Michitaka Ozaki[3], Masaru Konishi[1], Toshio Nakagohri[1] Shinichiro Takahashi[1], Takahito Yagi[2], Taira Kinoshita[1], Noriaki Tanaka[2]

[1]Department of Surgery, National Cancer Center Hospital East, Kashiwa;
[2]Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine and Dentistry Okayama; [3]Department of Organ Transplantation and Regenerative Medicine
Hokkaido University Graduate School of Medicine, Faculty of Medicine, Sapporo, Japan
Corresponding Author: Naoto Gotohda, MD, Department of Surgery, National Cancer Center Hospital East 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
Tel: +81 4 7133 1111, Fax: +81 4 7131 4724, E-mail: ngotohda@east.ncc.go.jp

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.

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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.

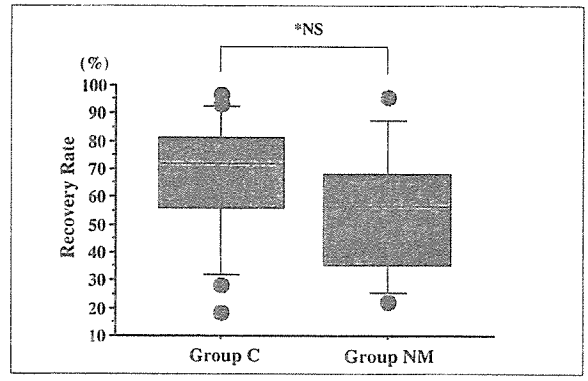

FIGURE 1 Percent recovery of liver size 4 weeks after hepatectomy. Percent recovery of liver size was calculated by volumetric analysis by resected liver volume, computed tomography of liver preoperatively and 4 wk after hepatectomy. *Statistical significance between groups was analyzed by Mann-Whitney's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

Comparison of Indocyanine Green Clearance with Child's-Pugh Score and Hepatic Histology: A Multivariate Analysis

Sandeep Mukherjee MD, Mary AM Rogers PhD, Borys Buniak MD
Liver Gallbladder Pancreas Center, Section of Gastroenterology and Hepatology, Department of Medicine
State University of New York Upstate Medical University, Syracuse, New York, USA
Corresponding Author: Sandeep Mukherjee, MD, Section of Gastroenterology and Hepatology
983285 Nebraska Medical Center, Omaha, NE 68198-3285, USA
Tel: +1 402 559 8859, Fax: +1 402 559 3434, E-mail: smukherj@unmc.edu

KEY WORDS:
Child's-Pugh score; Indocyanine green; Hepatic histology; Multivariate analysis

ABBREVIATIONS:
Indocyanine Green (ICG); Deoxyribonucleic Acid (DNA); Percentage Disappearance Rate (PDR); Ribonucleic Acid (RNA); Histological Activity Index (HAI); Polymerase Chain Reaction (PCR)

ABSTRACT

Background/Aims: Indocyanine green clearance, measured by percentage disappearance rate, detects alterations in liver function and may be used as a non-invasive determinant of hepatic reserve. The aims of this study were to compare liver histology and Child's-Pugh score with percentage disappearance rate and determine which variables correlated with PDR.

Methodology: Child's-Pugh score, liver function tests, liver biopsies and indocyanine green testing (0.5mg/kg) were performed in 102 consecutive patients with cirrhosis of diverse etiologies. Indocyanine green concentration was determined using spectrophotometric analysis (806nm) and plotted logarithmically with Michaelis-Menten kinetics to calculate the percentage disappearance rate. Liver biopsies were graded using the modified Knodell score to obtain a histological activity index.

Results: In bivariable analysis, percentage disappearance rate significantly correlated with Child's-Pugh score, albumin, bilirubin, prothrombin time and histological activity index. Albumin, prothrombin time and histological activity index were independent predictors of percentage disappearance rate in the final model (albumin $p<0.01$, prothrombin time $p<0.046$, histological activity index $p=0.033$), accounting for 46.2% of variability in percentage disappearance rate measurements.

Conclusions: Percentage disappearance rates correlated with Child's-Pugh scores in this series of cirrhotic patients. However, 46.2% of its variability was accounted for by albumin, prothrombin time and histological activity index.

INTRODUCTION

Chronic liver disease is a major health problem worldwide and for patients with end-stage liver disease, liver transplantation remains the treatment of choice. The Child's-Pugh score has traditionally been used to assess the severity of underlying disease although it is not a sensitive indicator of liver dysfunction (1). Patients may deteriorate before appreciable changes in their scores are recognized and to predict the need for liver transplantation or monitor hepatic response to therapy, a complementary test for quantification of liver function may be helpful.

Indocyanine green (ICG) is a tricarbocyanine dye strongly bound to albumin with high hepatic clearance by first order kinetics (70-90%). ICG does not undergo biotransformation or extrahepatic metabolism, is excreted unchanged in bile and does not undergo renal excretion (2,3). It has been used to measure liver blood flow and to quantify hepatic reserve in individuals with chronic liver disease (4-7). The aims of this study were to compare ICG clearance with the Child's-Pugh score and hepatic histology and determine which of these variables correlated with ICG clearance.

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METHODOLOGY

Patients: One hundred and two consecutive patients with cirrhosis were referred to a University hospital liver center for evaluation between 1995 and 1997. The mean age of patients was 49.7±13.4 years, of whom 51% were male and 49% female. Causes of cirrhosis in the study population are reported in **Table 1**.

Laboratory investigations: Blood samples were obtained for measurement of standard hepatic biochemical evaluations which included alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase, albumin, prothrombin time and total bilirubin. Hepatitis B surface antibody, hepatitis B e antigen, hepatitis B e antibody, hepatitis B core antibody, hepatitis B surface antibody were tested using commercially available enzyme-linked or radioimmunoassay test kits (Abbott Laboratories, North Chicago, IL). Hepatitis B DNA was detected using semiquantitative hybridization assay (Abbott Laboratories, North Chicago, IL). Hepatitis C antibody was obtained using second-generation enzyme-linked immunoassay (Abbott Laboratories, North

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Selection Criteria for Reduction Hepatectomy in Multiple Advanced Hepatocellular Carcinoma

NAOTO GOTOHDA[1], HIROSHI ISHII[2], MASARU KONISHI[1], TOSHIO NAKAGOHRI[1], SHINICHIRO TAKAHASHI[1], JUNJI FURUSE[2], MASAHIRO YOSHINO[2] and TAIRA KINOSHITA[1]

[1]Department of Hepatobiliary Pancreatic Surgery and [2]Department of Hepatobiliary Pancreatic Medical Oncology, National Cancer Center Hospital East, Chiba, 277-8577, Japan

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.

Correspondence to: Naoto Gotohda, MD, Department of Hepatobiliary Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan. Tel: +81 4 7133 1111, Fax: +81 4 7131 4724, e-mail: ngotohda@east.ncc.go.jp

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*.

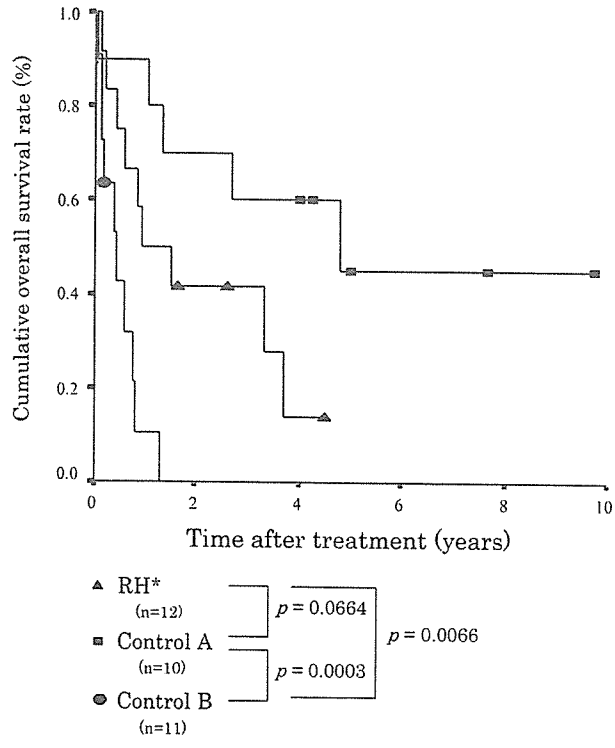

Figure 1. *Kaplan-Meier estimated survival curves according to treatment in patients with tumor extension in >50% of liver. *RH: reduction hepatectomy. Statistical significance was analyzed by log-rank test.*

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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