Patients who experience recurrence after LT show rapid progression of recurrent disease and have a very poor prognosis because the rate of progression of recurrent HCC is more rapid after transplantation than after hepatic resection (*11, 12*). However, some patients have a good prognosis if they are appropriately treated after recurrence. Hence, it is important to predict not only who is likely to exhibit recurrence but also who may survive longer. There are no reports about the relationship between NLR and patients with recurrent HCC after LDLT, and there is little information regarding prognosis and treatment for HCC recurrence after LT. Therefore, in this study, we investigated the relationship between preoperative and postoperative NLR and prognosis of patients with recurrent HCC after LDLT.

RESULTS

In total, HCC recurrence was identified in 26 (15.5%) patients: 16 men and 10 women among the 167 patients with HCC. The mean duration until the initial recurrence after LDLT was 3.7 years, and the mean duration until death the initial recurrence was 1.7 years. Clinicopathologic factors on recurrence of HCC after LDLT using univariate analysis are shown in Table 1 and Table S1 (see **SDC**, http://links.lww.com/TP/A868). AFP ≧300 ng/mL, DCP ≧300 mAU/mL, NLR ≧4, tumor number >3, tumor size ≧5 cm, duration of last treatment of HCC to LDLT <3 months, Milan criteria exceeded, histologic tumor number ≧10, histologic tumor size >5 cm, poor differentiation, presence of histologic vascular invasion, adjuvant chemotherapy, and interferon (IFN) therapy against patients with hepatitis C virus (HCV) were significant differences between patients with recurrence and without recurrence of HCC. There were no significant differences regarding host-related factors except IFN between the two groups.

The prognostic factors for survival after recurrence using univariate analysis are shown in Table 2. These data included both factors before LDLT (Table 2) and those after LDLT (Table 3). Male sex, IFN therapy against patients with HCV, AFP ≧300 ng/mL at recurrence, NLR ≧4 at recurrence, and nonsurgical resection for recurrent HCC were significantly related to poor prognosis. The survival curves after recurrence for the patients with NLR ≧4 at recurrence are illustrated in Figure 1. The 3-year survival curves after recurrence were 0% in patients with NLR ≧4 and 43.6% in patients with NLR <4. The 3-year survival curves after recurrence were 50% in females and 9.5% in males, whereas the 3-year survival curves after recurrence were 53.3% in patients with IFN therapy against HCV and 0% in patients without IFN therapy. Furthermore, the 3-year survival curve after recurrence were 0% in patients with AFP ≧300 ng/mL at recurrence and 28.4% in patients with AFP <300 ng/mL. The 3-year survival curves after recurrence were 41.7% in patients with surgical resection for recurrent HCC and 0% in patients without surgical resection for recurrent HCC. Interestingly, AFP and NLR before LDLT, in particular, were not related to survival after recurrence of HCC. Multivariate analysis was not performed because of the small sample size.

NLR was reelevated after LDLT in patients who later died, whereas NLR gradually decreased in surviving patients (Fig. 2).

DISCUSSION

Using univariate analysis, our retrospective study indicated that male sex, IFN therapy for HCV, NLR and AFP at recurrence, and surgical resection for recurrent HCC were poor prognostic factors for survival after recurrence of HCC among patients with LDLT. We recently proposed new selection criteria for LDLT in patients with HCC (*7*). A multivariate analysis identified independent risk factors for post-LDLT tumor recurrence including tumor size, the presence of eight or more tumors, and an NLR of 4 or more. These criteria could effectively exclude patients with biologically

TABLE 1. Patients and tumor characteristics between patients with recurrence and without recurrence of HCC

Factors	Patients with recurrent HCC (n=26)	Patients without recurrent HCC (n=141)	*P*
AFP (ng/mL) <300/≧300	12/14	126/15	0.001
DCP (mAU/mL) <300/≧300	12/14	122/19	0.001
NLR <4/≧4	16/10	125/16	0.001
Number of tumors ≦3/>3	16/10	108/33	0.002
Tumor size (cm) ≦5/>5	6/20	139/2	0.001
Duration of last treatment to LDLT			
<3/≧3 months	16/10	127/14	0.001
Milan criteria, yes/No	7/19	98/43	0.001
Number of tumors (histologic)			
<10/≧10	13/13	114/27	0.002
Tumor size (cm) (histologic)			
≦5/>5	9/17	137/4	0.001
Tumor differentiation (histologic)			
Well+moderate/poor	16/10	111/30	0.001
Vascular invasion (histologic)			
Yes/no	18/8	40/101	0.001
IFN			
Yes/no	8/11	69/30	0.032

TABLE 2. Clinicopathologic factors on survival after recurrence of HCC using univariate analysis

Factors before LDLT	Patients	Survival at 3 years (%)	P
Gender			
Male	**16**	9.5	0.006
Female	10	50.0	
Age (years)			
≦57	12	13.0	0.943
>57	14	36.5	
Hepatitis			
HCV	19	20.2	0.489
Non-HCV	7	45.7	
Child-Pugh classification			
A+B	14	0	0.066
C	12	44.2	
MELD score			
<15	21	34.2	0.157
≧15	5	0	
AFP (ng/mL)			
<300	14	32.7	0.709
≧300	12	15.6	
DCP (mAU/mL)			
<300	14	35.0	0.185
≧300	12	16.7	
NLR			
<4	16	26.7	0.981
≧4	10	24.2	
Number of tumors			
≦3	10	33.3	0.613
>3	16	25.0	
Tumor size (cm)			
≦5	20	28.4	0.818
>5	6	16.7	
Duration of initial HCC to LDLT			
<1 year	7	16.2	0.509
≧1 year	15	28.6	
Duration of last treatment to LDLT			
<3 months	16	35.4	0.191
≧3 months	10	11.1	
Milan criteria			
Yes	7	60.0	0.481
No	19	21.1	
Graft vs. standard liver volume (%)			
<35	6	29.6	0.976
≧35	20	20.8	
Age of donor (year)			
≦30	11	15.0	0.926
>30	15	36.2	

aggressive tumors before LT, promoting an extremely low recurrence rate.

The rate of HCC recurrence after transplantation has ranged from 8% to 22.7% in different studies (*13–16*). Patients who experience recurrence after LT show rapid progression of recurrent disease and have a very poor prognosis such that median survival after recurrence ranged from 7 to 9 months because the rate of progression of recurrent HCC is more rapid after transplantation than after hepatic resection (*15, 17*). The main reason for this poor outcome is that the progression of the disease is usually fast because of the immunosuppressed state after transplantation. However, some patients have a good prognosis if they are appropriately treated after recurrence. In this study, NLR and AFP at recurrence are useful biomarkers to predict the prognosis after

TABLE 3. Clinicopathologic factors on survival after recurrence of HCC using univariate analysis

Factors after LDLT	Patients	Survival at 3 years (%)	P
Number of tumors (histologic)			
<10	13	42.9	0.102
≧10	13	10.0	
Tumor size (cm) (histologic)			
≦5	17	28.6	0.488
>5	9	22.2	
Tumor differentiation (histologic)			
Well+moderate	10	27.8	0.819
Poor	16	11.5	
Vascular invasion (histologic)			
Yes	18	19.7	0.446
No	8	38.1	
Adjuvant chemotherapy			
Yes	11	27.3	0.630
No	15	25.0	
CNI			
CyA	13	18.2	0.653
Tac	13	32.3	
Steroid use			
Yes	17	14.1	0.134
No	9	42.9	
IFN against HCV			
Yes	9	53.3	0.013
No	11	0	
AFP (ng/mL) at recurrence			
<300	23	28.4	0.001
≧300	3	0	
DCP (mAU/mL) at recurrence			
<300	21	31.4	0.120
≧300	5	0	
NLR at recurrence			
<4	17	43.6	0.006
≧4	9	0	
Initial site of recurrence			
Liver	4	33.3	0.986
Extraliver	22	22.6	
Duration of LDLT to recurrence (years)			
>1	12	40.0	0.097
≧1	14	12.2	
Surgical resection for recurrent HCC			
Yes	14	41.7	0.002
No	12	0	

recurrent HCC. This is the first report to discuss the relationship between NLR and the prognosis in patients with recurrent HCC after LDLT.

It is difficult to treat recurrences because these tumors tend to be involved in multiple organs, and if the tumor recurs in a single organ, it usually manifests multiple lesions. These findings suggest that the aggressiveness of the tumor and the effectiveness of the treatment for the recurrent lesion were important to survival after recurrence. If the recurrent disease progressed slowly and if the recurrent lesion was locally controllable, patient survival could be prolonged. Hence, it is important to predict not only who may live but also who can survive longer after recurrence.

Roayaie et al. (*15*) described that the surgical treatment of recurrence was independently associated with significantly longer survival. Furthermore, several articles suggested that surgical treatment of recurrent tumors after LT should be considered whenever possible (*14–16*). However, the indications for surgical resection of recurrent HCC are a solitary tumor or curative resection; thus, there is possibility that the patient whose recurrence had more malignant behavior (multiple recurrence or multisite recurrence) was eliminated as a candidate of surgical treatment. Interestingly, none of the primary tumor characteristics were associated with survival after HCC recurrence. There was no association of the survival after recurrence such as tumor size, number of tumors, tumor marker at pre-LT, histologic differentiation, or vascular invasion. Schlitt et al. (*16*) also reported that no primary tumor characteristics were associated with survival after HCC recurrence. These findings suggest that the malignant phenotype of the recurrent HCC might be quite different from that of the primary HCC. In our study, a univariate analysis showed that sex, IFN therapy for HCV, AFP ≧300 ng/mL at recurrence, NLR ≧4 at recurrence, and surgical resection were significant factors for recurrent HCC. Tumor growth in recurrent HCC is quicker after LT mainly because of the need for permanent immunosuppression (*17*). NLR and AFP at recurrence may reflect the biological malignant behavior.

The molecular mechanism associated with elevated NLR and the prognosis of patients with HCC is associated with many factors, but it remains poorly understood. Chronic systemic inflammation is an important prognostic factor in patients with cancer. The NLR was used as a parameter of chronic inflammation in patients with cancer. We previously showed that NLR was an important prognostic factor in patients with HCC after hepatic resection (*9*) and in patients who underwent LDLT (*10*). A close relationship between accumulation of tumor-associated macrophages in HCC and high NLR levels was observed in patients with HCC who underwent hepatic resection and LDLT (*18*). A high NLR is associated with a high infiltration of tumor-associated macrophages and high inflammatory cytokine production in the tumor, such as interleukin-6 and interleukin-8, which promote systemic neutrophilia.

In conclusion, this retrospective analysis revealed that NLR at recurrence is a prognostic factor affecting survival after recurrence in LDLT for HCC. A multi-institutional study is needed to provide evidence of the significance of NLR in HCC.

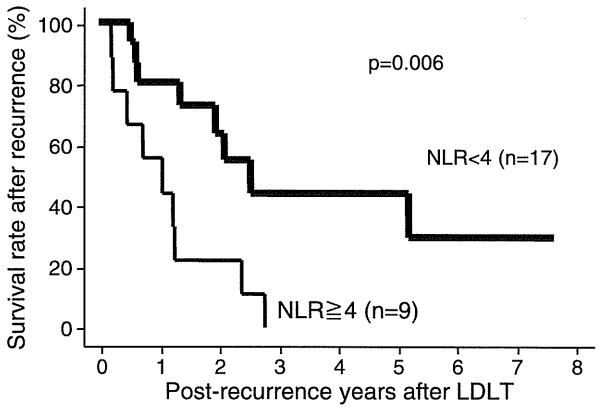

FIGURE 1. Survival after recurrence in patients with NLR<4 at recurrence or those with NLR≧4 at recurrence. Survival after recurrence in patients with NLR≧4 at recurrence was significantly poor prognosis.

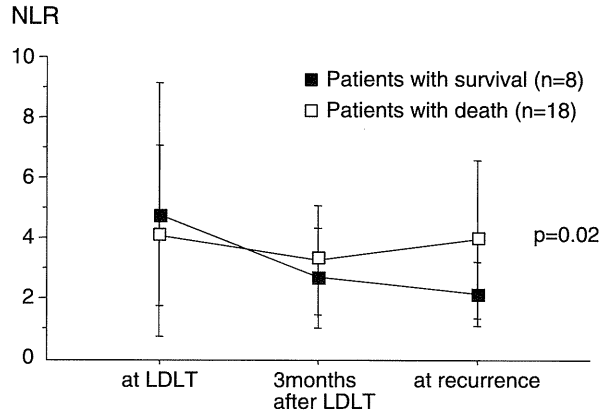

FIGURE 2. Time-dependent NLR at LDLT, 3 months after LDLT, and at recurrence. □, patients with death; ■, patients with survival. NLR was reelevated after LDLT in patients with death; on the contrary, NLR was gradually decreased with patients with survive.

MATERIALS AND METHODS

Patient Characteristics

A total of 393 LDLT operations were performed at Kyushu University Hospital from October 1996 to August 2012 after approval was obtained from the Ethics and Indications Committee of Kyushu University. Among them, 167 adult-to-adult LDLTs for HCC were enrolled in this study. The selection criteria for the HCC patients were as follows: (a) no modality, except LDLT available to cure patients with HCC and end-stage liver disease; (b) no extrahepatic metastasis; and (c) no major vascular infiltration, such as the portal vein or hepatic vein, thus indicating that there was no restriction on the tumor size or the number of the tumors.

The transplant procedures for both the donors and recipients have been described previously (*6*). The immunosuppressive regimen consisted of the combination of a calcineurin inhibitor (CNI) (tacrolimus [Tac] or cyclosporine A [CyA]) and steroid with or without mycophenolate mofetil. A steroid injection was given intravenously (methylprednisolone 1 g) and tapered to zero by day 7. Mycophenolate mofetil (1 g/day) treatment was started from postoperative day 1 and completed by 3 months. A maintenance immunosuppression therapy was conducted with low-dose Tac or CyA from postoperative day 7. Adjuvant systemic chemotherapy using 5-fluorouracil

and cisplatin with or without gemcitabine for 1 month were administered to patients who had more than 300 mAU/mL DCP, more than 5 cm of maximum tumor size, or who exceeded the Milan criteria.

Prognostic Factor

The prognostic factors were examined with respect to survival after recurrence of HCC based on the following variables: sex (male vs. female), age (≧57 vs. <57 years), hepatitis (HCV vs. non-HCV), Child-Pugh classification (A+B vs. C), the Model for End-Stage Liver Disease (MELD) score (<15 vs. ≧15), serum AFP level (≧300 vs. <300 ng/mL), DCP level (≧300 vs. <300 mAU/L), NLR (≧4.0 vs. <4.0), number of tumors (≦3 vs. >3), tumor size (≦5 vs. >5 cm), duration of initial HCC to LDLT (<1 vs. ≧1 year), duration of last treatment to LDLT (<3 vs. ≧3 months), Milan criteria (yes vs. no), graft vs. standard liver volume (<35% vs. ≧35%), age of donor (<30 vs. >30 years), histologic number of tumors (<10 vs. ≧10), histologic tumor size (≦5 vs. >5 cm), histologic tumor differentiation (well+moderate vs. poor), histologic vascular invasion (yes vs. no), adjuvant chemotherapy (yes vs. no), CNI (CyA vs. Tac), steroid use (yes vs. no), IFN against HCV (yes vs. no), AFP level at recurrence (≧300 vs. <300 ng/mL), DCP level at recurrence (≧300 vs. <300 mAU/L), NLR at recurrence (≧4.0 vs. <4.0), initial site of recurrence (liver vs. extraliver), duration of LDLT to recurrence (<1 vs. ≧1 year), and surgical resection for recurrent HCC (yes vs. no).

Patient Follow-up

The clinical follow-up of patients transplanted for HCC followed a strict protocol, which did not change during the study period. The patients were seen biweekly for the first month and then screened monthly for 6 months for tumor markers such as AFP and DCP. The patients had ultrasound scans and enhanced computed tomography scans at 6-month intervals. When recurrence was suspected, additional examination such as hepatic angiography were performed. The median follow-up period was 3.9 years.

Treatment of HCC Recurrence

Patients with recurrence that could be surgically cured underwent a resection or ablation of their tumors. All patients considered to be unsuitable for surgical treatment were referred for palliative care by radiotherapy, transarterial chemoembolization, and administration of 5-fluorouracil–based systemic therapy.

Histologic Study

All of the resected specimens were cut into serial 5- to 10-mm-thick slices and fixed in 10% formalin. After macroscopic examination, the slice with the greatest dimensions was trimmed for embedding in paraffin and cut into 4-μm microscopic sections. The sections were stained with hematoxylin-eosin. Tumor differentiation, microvascular invasion, intrahepatic metastasis, and histologic liver cirrhosis were examined by the pathologist according to the Liver Cancer Study Group in Japan (*19*).

Statistical Analysis

We analyzed the categorical clinicopathologic variables using the chi-square test or Fisher's exact test. Continuous variables were expressed as means and SDs and compared with the Student's *t* test. The survival curves after recurrence of the two groups were analyzed by the Kaplan–Meier method and compared with the log-rank test. All analyses were performed with Statview 5.0 software (Abacus Concepts, Berkeley, CA). NLR in a subsequent phase were compared by repeated-measures analysis of variance. $P<0.05$ was considered statistically significant.

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Original article

Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma

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Background: **Sarcopenia was identified recently as a poor prognostic factor in patients with cancer. The present study investigated the effect of sarcopenia on short- and long-term outcomes following partial hepatectomy for hepatocellular carcinoma (HCC), and aimed to identify prognostic factors.**

Methods: **Data were collected retrospectively for all consecutive patients who underwent hepatectomy for HCC with curative intent between January 2004 and December 2009. Patients were assigned to one of two groups according to the presence or absence of sarcopenia, assessed by computed tomographic measurement of muscle mass at the level of the third lumbar vertebra. Clinicopathological, surgical outcome and long-term survival data were analysed.**

Results: **Sarcopenia was present in 75 (40·3 per cent) of 186 patients, and was significantly correlated with female sex, lower body mass index and liver dysfunction, as indicated by abnormal serum albumin levels and indocyanine green retention test at 15 min values. In patients with, and without sarcopenia, the 5-year overall survival rate was 71 and 83·7 per cent respectively, and the 5-year recurrence-free survival rate was 13 and 33·2 per cent respectively. Multivariable analysis revealed that reduced skeletal muscle mass was predictive of an unfavourable prognosis.**

Conclusion: **Sarcopenia was predictive of worse overall survival even when adjusted for other known predictors in patients with HCC after partial hepatectomy.**

Paper accepted 8 July 2013

Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9258

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world[1,2]. As a consequence of advances in the diagnosis and management of HCC, major improvements in overall and disease-free survival rates for HCC after partial hepatectomy have been achieved. However, even when curative resection is performed, a considerable number of patients develop intrahepatic or extrahepatic recurrence[3,4]. The prognostic assessment of patients with HCC after hepatic resection and recurrence is an important clinical issue in this population[5–7]. Both tumour- and host-related factors are related to clinical outcome, and general condition and liver function are important in this context. Unfortunately, it is difficult to evaluate the general condition of patients excluding liver function before hepatectomy. Conventional methods, such as the Child–Pugh classification, have been used initially to determine the severity of cirrhosis and to select patients who might tolerate hepatic resection. However, these methods do not reflect the patient's general condition. The American Society of Anesthesiologists (ASA) grade was reported to predict the prognosis of HCC after hepatectomy[8], but this classification is not always objective.

Recently, loss of skeletal muscle mass, termed sarcopenia, was identified as a poor prognostic factor for patients with pancreatic cancer, colorectal liver metastases, melanoma, liver cirrhosis and liver transplantation[9–14]. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor quality of life and death[15,16]. To date, there have been no reports on the relationship between sarcopenia and the prognosis of patients with HCC following hepatic resection.

A retrospective study was performed at the authors' institution to investigate the outcome of patients with sarcopenia who underwent hepatic resection for HCC. The outcome of these patients was compared with that of patients without sarcopenia undergoing hepatic resection during the same period.

Methods

All patients who underwent hepatic resection with curative intent as the initial treatment in the Department of Surgery II, Kyushu University Hospital, between January 2004 and December 2009 were enrolled in the study. Curative resection was defined as complete macroscopic removal of the tumour. All patients had preoperative computed tomography (CT). A transverse CT image at the third lumbar vertebra (L3) in the inferior direction was assessed from each scan. Skeletal muscle was identified and quantified by Hounsfield unit (HU) thresholds of −29 to +150 (water is defined as 0 HU, air as 1000 HU). Multiple muscles were quantified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscle, and rectus abdominis muscle (*Fig. 1*). CT measurements were calibrated with water and air at fixed intervals. Cross-sectional areas (cm^2) of skeletal muscles in the L3 region were measured by manual outlining on the CT images, and checked by the radiologist. The cross-sectional areas were then normalized for height (cm^2/m^2).

Cut-off values for skeletal muscle associated with overall survival were defined as 43·75 cm^2/m^2 for men and 41·10 cm^2/m^2 for women[10]. Based on this cut-off, patients were assigned to one of two groups, depending on the presence or absence of sarcopenia. The clinicopathological background and rates of overall and recurrence-free survival were compared between the two groups.

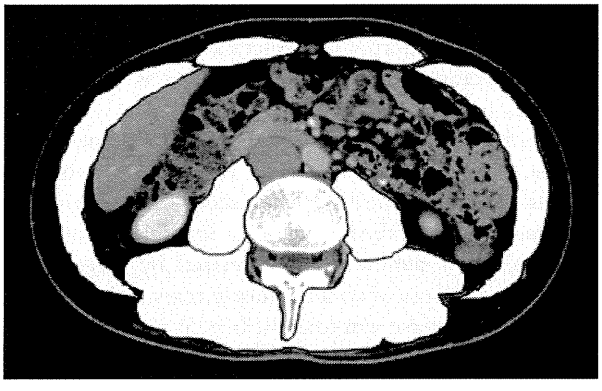

Fig. 1 Computed tomogram showing the area of skeletal muscle mass in the L3 region (highlighted yellow)

The prognostic factors were examined with respect to overall and recurrence-free survival on the basis of the following variables: sarcopenia (absence *versus* presence); skeletal muscle mass; age; sex (male *versus* female); body mass index (BMI); hepatitis B surface antigen (positive *versus* negative), hepatitis C virus antibody (positive *versus* negative); serum albumin level; serum total bilirubin level; serum aspartate aminotransferase level; platelet number; indocyanine green retention test at 15 min (ICGR15); Child–Pugh grade (A *versus* B); Model for End-Stage Liver Disease (MELD) score; histological liver cirrhosis (normal liver + chronic hepatitis *versus* liver fibrosis and liver cirrhosis); tumour size; tumour number (solitary *versus* multiple); tumour node metastasis (TNM) stage according to the Liver Cancer Study Group of Japan[17] (I + II *versus* III + IV); tumour differentiation (well differentiated + moderately differentiated *versus* poorly differentiated); microvascular invasion (MVI) (absence *versus* presence); intrahepatic metastases (absence *versus* presence); serum α-fetoprotein level (AFP); des-γ-carboxyprothrombin (DCP) level; operative procedure (anatomical *versus* non-anatomical resection); duration of surgery; estimated blood loss; and postoperative complications (absence *versus* presence). Patients with diabetes were defined as those using an oral hypoglycaemic agent or insulin. The MELD score was calculated in accordance with a previous report[18]. Postoperative complications within 1 month after partial hepatectomy included liver failure, encephalopathy, gastrointestinal bleeding, intraperitoneal abscess, abdominal haemorrhage, bile leakage, pleural effusion, intractable ascites and wound infection. Complications were classified according to Clavien–Dindo[19]; grade III complications (those requiring surgical intervention) were considered to indicate the presence of a postoperative complication.

Surgical procedures

Details of surgical techniques and patient selection criteria have been reported previously[7]. Selection criteria for hepatic resection were: ascites not detected, or controllable by diuretics; serum total bilirubin level lower than 2·0 mg/ml; and ICGR15 value below 40 per cent. The surgical approach included a J-shaped incision for routine abdominal access, hepatic dissection using an ultrasonic dissector with a coagulator (CUSA EXcel®; Integra, Plainsboro, New Jersey, USA), with systematic ligation of all sizable vessels, and close ultrasonographic guidance along the transection line. Cholecystectomy was performed

in all patients if applicable. An intraoperative bile leak test was performed routinely[20]. Small bile leaks on the cut liver surface were repaired by Z-suturing with 6-0 polydioxanone (PDS II; Johnson and Johnson, Tokyo, Japan). Intraoperative vascular control was achieved with the Pringle manoeuvre[21].

Follow-up strategy and recurrence pattern

After discharge, all patients were examined monthly for recurrence by ultrasonography and estimation of tumour markers, such as AFP and DCP, and by CT every 6 months. When recurrence was suspected, additional examinations such as hepatic angiography were performed. Recurrent HCC was treated by repeat hepatectomy, ablation therapy and lipiodolization, as described previously[22].

Histological assessment

All resected specimens were cut into serial 5–10-mm thick slices and fixed in 10 per cent formalin. After macroscopic examination, the slice with the greatest dimensions was trimmed for embedding in paraffin and cut into 4-μm microscopic sections. The sections were stained with haematoxylin and eosin. Tumour differentiation, MVI, intrahepatic metastases and histological liver cirrhosis were assessed by the pathologist in accordance with the rules of the Liver Cancer Study Group of Japan[17].

Table 1 Clinicopathological factors in patients with, and without sarcopenia

	Sarcopenia ($n = 75$)	No sarcopenia ($n = 111$)	P†
Age (years)	67(11)	66(10)	0·553
Sex ratio (M : F)	50 : 25	95 : 16	0·004‡
Skeletal muscle mass (cm^2/m^2)	37·8(3·7)	49·7(6·5)	<0·001
Body mass index (kg/m^2)	20·5(2·4)	24·0(2·8)	<0·001
Diabetes mellitus	22 (29)	35 (31·6)	0·999‡
Albumin (g/dl)	3·8(0·4)	4·0(0·4)	0·002
Total bilirubin (mg/dl)	0·9(0·4)	0·8(0·3)	0·096
Platelet count ($\times 10^4/\mu l$)	15·5(7·5)	16·3(6·2)	0·454
ICGR15 (%)	15·7(8·2)	13·6(6·2)	0·049
Child–Pugh grade			0·190‡
A	68 (91)	107 (96·4)	
B	7 (9)	4 (3·6)	
MELD score	7·7(2·1)	7·9(1·8)	0·591
Hepatitis grade			0·652‡
None	11 (15)	13 (11·7)	
Mild	55 (73)	80 (72·1)	
Severe	9 (12)	18 (16·2)	
Liver cirrhosis			0·290‡
Normal liver + chronic hepatitis	32 (43)	55 (49·5)	
Liver fibrosis + liver cirrhosis	43 (57)	56 (50·5)	
Tumour size (cm)	4·0(3·2)	3·9(2·8)	0·770
No. of tumours			0·171‡
Solitary	52 (69)	88 (79·3)	
Multiple	23 (31)	23 (20·7)	
TNM stage			0·967‡
I	11 (15)	18 (16·2)	
II	38 (51)	57 (51·4)	
III	20 (27)	29 (26·1)	
IV	6 (8)	7 (6·3)	
Differentiation of HCC			0·690‡
Well	9 (12)	10 (9·0)	
Moderate	50 (67)	77 (69·4)	
Poor	16 (21)	24 (21·6)	
Microvascular invasion	24 (32)	37 (33·3)	0·890‡
Intrahepatic metastases	12 (16)	18 (16·2)	0·978‡
α-Fetoprotein level (ng/ml)	3459(18 300)	12 250(70 470)	0·297
DCP (munits/l)	4318(13 627)	2942(12 499)	0·480
Postoperative complications	24 (32)	56 (50·5)	0·613‡

Values are mean(s.d.) unless indicated otherwise: *values in parentheses are percentages. ICGR15, indocyanine green dye retention test at 15 min; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis (stage defined by the Liver Cancer Study Group of Japan); HCC, hepatocellular carcinoma; DCP, des-γ-carboxyprothrombin. †Mann–Whitney U test, except ‡Fisher's exact test or χ^2 test.

Statistical analysis

Associations of continuous and categorical variables with relevant outcome variables were assessed using the Mann–Whitney *U* test and Fisher's exact test respectively. The variable skeletal muscle was not *a priori* categorized into a binary variable (sarcopenia present or not), because categorizing a continuous predictor would result in an inevitable loss of information. Instead, the multivariable fractional polynomial (MFP) approach was adopted. In the polynomial fractional model, for each continuous variable X, one or two terms of the form X^p were fitted with powers, p, chosen from (−2, −1, −0·5, 0, 0·5, 1, 2 and 3). The results of the MFP analysis revealed that the most appropriate power for skeletal muscle mass in the MFP model was given in the form of X (that is, $p = 1$), allowing expression of a final multivariable model in terms of the usual Cox regression model. Therefore, the results of the usual Cox model are reported here, giving the results of the log rank tests for the association between the presence of sarcopenia (as defined by dichotomizing skeletal muscle mass) and overall or disease-free survival[23]. To identify prognostic factors after hepatectomy, all variables were included in the overall multivariable Cox proportional model in the analyses of both overall and recurrence-free survival using the backward selection method. The overall and recurrence-free survival curves were analysed by the Kaplan-Meier method and compared with the log rank test. All analyses were performed with StatView® 5.0 software (Abacus Concepts, Berkeley, California, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

In total, 186 patients with HCC were identified from the database, of whom 75 (40·3 per cent; 50 men and 25 women) had sarcopenia. Clinicopathological characteristics of patients with and without sarcopenia are shown in *Table 1*. Women were more likely to have sarcopenia than men. Patients with sarcopenia had a significantly lower BMI than those without. Regarding liver function, serum albumin levels were significantly lower and ICGR15 values were significantly higher in patients with sarcopenia than in those without. Other host-related factors such as age, hepatitis, diabetes mellitus, Child–Pugh grade, MELD score and liver cirrhosis were not related to the presence of sarcopenia. There were no significant differences in tumour-related factors or surgical outcomes between the two groups. Operative details are shown in *Table S1* (supporting information).

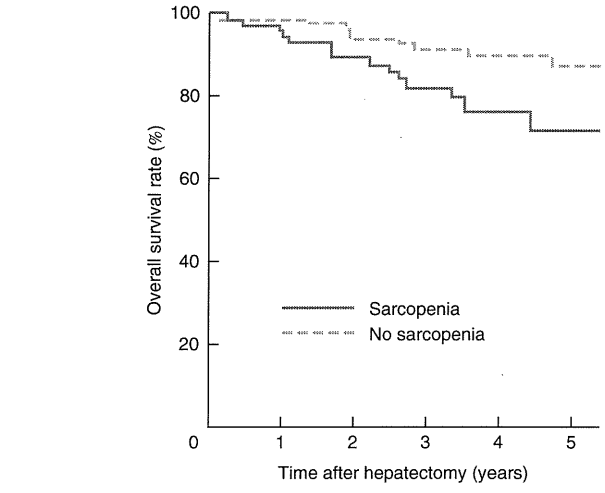

Fig. 2 **a** Overall and **b** recurrence-free survival curves after liver resection in patients with, and without sarcopenia. **a** $P = 0{\cdot}001$, **b** $P = 0{\cdot}013$ (log rank test)

Overall and recurrence-free survival curves for patients with and without sarcopenia are shown in *Fig. 2*. Overall and recurrence-free 5-year survival rates were 71 and 13 per cent respectively in patients with sarcopenia, and 83·7 and 33·2 per cent in patients without sarcopenia (*Fig. 2*). Patients with sarcopenia had a significantly worse prognosis

Table 2 Univariable and multivariable analysis of clinicopathological factors and overall survival following partial hepatectomy with curative intent for hepatocellular carcinoma

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P**	Hazard ratio	*P*†
Age	1·02 (0·98, 1·07)	0·323		
Female sex	1·17 (0·42, 2·79)	0·746		
Skeletal muscle mass	0·92 (0·86, 0·97)	0·004	0·90 (0·84, 0·96)	0·002
Body mass index	0·92 (0·81, 1·04)	0·199		
Albumin	0·47 (0·21, 1·14)	0·092		
ICGR15	1·02 (0·97, 1·07)	0·512		
MELD score	1·08 (0·86, 1·25)	0·460		
Liver fibrosis + cirrhosis	3·97 (1·50, 13·67)	0·004		
Tumour size	1·10 (0·98, 1·22)	0·906		
Multiple tumours	1·60 (0·65, 3·64)	0·292		
TNM stage III + IV	1·62 (0·70, 3·62)	0·255		
Poor differentiation	2·26 (0·98, 5·16)	0·055	2·47 (1·05, 5·81)	0·021
Microvascular invasion	2·39 (1·05, 5·41)	0·038	3·21 (1·29, 7·94)	0·018
Intrahepatic metastases	1·67 (0·55, 4·15)	0·333		
α-Fetoprotein	1·00 (1·00, 1·00)	0·335		
DCP	1·00 (1·00, 1·00)	0·267		
Postoperative complications	2·76 (1·23, 6·28)	0·014	3·27 (1·39, 7·69)	0·007

Values in parentheses are 95 per cent confidence intervals. ICGR15, indocyanine green dye retention test at 15 min; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis; DCP, des-γ-carboxyprothrombin. *Log rank test; †Cox proportional model.

Table 3 Univariable and multivariable analysis of clinicopathological factors and recurrence-free survival following partial hepatectomy with curative intent for hepatocellular carcinoma

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P**	Hazard ratio	*P*†
Age	1·01 (1·00, 1·04)	0·139		
Female sex	1·02 (0·63, 1·59)	0·918		
Skeletal muscle mass	0·98 (0·95, 1·00)	0·049	0·97 (0·95, 1·00)	0·016
Body mass index	0·94 (0·88, 1·02)	0·076		
Albumin	0·49 (0·33, 0·75)	0·001		
ICGR15	1·03 (1·01, 1·06)	0·048	1·02 (1·02, 1·07)	0·001
MELD score	1·03 (0·93, 1·12)	0·526		
Liver fibrosis + cirrhosis	1·98 (1·32, 3·01)	0·001		
Tumour size	1·00 (0·98, 1·11)	0·141		
Multiple tumours	1·89 (1·22, 2·84)	0·005		
TNM stage III + IV	2·44 (1·64, 3·61)	0·001	2·13 (1·38, 3·29)	0·001
Poor differentiation	1·58 (1·04, 2·35)	0·033		
Microvascular invasion	2·39 (1·05, 5·41)	0·038		
Intrahepatic metastases	2·14 (1·30, 3·38)	0·003	2·37 (1·38, 4·06)	0·018
α-Fetoprotein	1·00 (1·00, 1·00)	0·001		
DCP	1·00 (1·00, 1·00)	0·006	1·00 (1·00, 1·00)	0·001
Postoperative complications	1·11 (0·73, 1·67)	0·617		

Values in parentheses are 95 per cent confidence intervals. ICGR15, indocyanine green dye retention test at 15 min; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis; DCP, des-γ-carboxyprothrombin. *Log rank test; †Cox proportional model.

than those without in terms of both overall ($P = 0·001$) and recurrence-free survival ($P = 0·013$).

In univariable analysis, significant prognostic factors for overall survival were low skeletal muscle mass, and presence of liver cirrhosis, MVI and postoperative complications (*Table 2*). Significant prognostic factors for recurrence-free survival were lower skeletal muscle mass, serum albumin level, liver cirrhosis, tumour number, tumour stage, poorly differentiated HCC, MVI, intrahepatic metastases, and serum AFP and DCP levels (*Table 3*). Multivariable analysis identified four poor prognostic factors (low skeletal muscle mass, poorly differentiated HCC, MVI and postoperative complications) that influenced overall survival, and five poor prognostic factors (low skeletal muscle mass, high

ICGR15 value, high serum DCP level, presence of intrahepatic metastases, and stage III + IV disease) that influenced recurrence-free survival (*Tables 2* and *3*).

Discussion

The findings of this retrospective single-centre study suggest that sarcopenia is an independent prognostic factor for overall and recurrence-free survival in patients with HCC following partial hepatectomy. The Child–Pugh classification was the first systematic and conventional approach used to determine the severity of cirrhosis and select patients who might tolerate hepatic resection. However, it is not always a reliable indicator of hepatic reserve, and has a limited role in predicting postoperative outcome[24]. The MELD score is a reliable measure of mortality risk in patients with end-stage liver disease and is suitable for use as a disease severity index to determine organ allocation priorities. No useful, objective, easily obtained and precise marker has yet been identified to evaluate the general condition of patients before hepatectomy. The ASA grade gives an estimation of organ disease and functional status, and has been suggested as a useful prognostic factor for preoperative patients with HCC[8]. However, it has been criticized for being subjective and imprecise[16].

Sarcopenia is defined as muscle mass two standard deviations below the mean in healthy young adults[25]. Although sarcopenia is associated with ageing, it can also develop as a consequence of chronic disease and malignancy. The European Working Group on Sarcopenia in Older People[15] recommended using the presence of both low muscle mass and low muscle function for the diagnosis of sarcopenia. However, muscle function is difficult to evaluate, and thus low muscle mass was investigated in the present study. There was no correlation between sarcopenia and age, but sarcopenia was significantly correlated with liver dysfunction as indicated by abnormal serum albumin levels and ICGR15 values, as well as with reduced BMI values. There was no correlation between sarcopenia and the Child–Pugh classification, MELD score or liver cirrhosis. There are some reports that serum albumin levels are decreased in patients with sarcopenia[26], which could be an early warning sign of subclinical conditions and impending disease and disability. Montano-Loza and colleagues[12] reported that, of patients with cirrhosis, those with sarcopenia had a significantly lower BMI than patients without sarcopenia. Liver cirrhosis was observed in 50 per cent of patients in their study, in line with the present findings. There is no report concerning the relationship between ICGR15 values and sarcopenia. In one study[12], skeletal muscle area was correlated with MELD score, which would seem to contradict the present findings; however, the mean MELD score was better in the present study, perhaps explaining these findings.

CT is the standard procedure for quantifying skeletal muscle mass, enabling objective and detailed nutritional and metabolic assessment of patients. Moreover, CT is always performed before hepatectomy, allowing precise assessment of sarcopenia. There are some reports that muscle mass as measured by CT is associated with the prognosis of sarcopenia.

It has been suggested previously that surgical outcomes are worse for obese patients[27]; however, there are few reports concerning the effect of being underweight on patient outcomes following hepatectomy for HCC. In this study, lower BMI was correlated with sarcopenia but not with the prognosis. BMI was significantly lower in sarcopenic patients, although only five patients were considered to be underweight (BMI below 18·5 kg/m^2). Thus, sarcopenia is not present exclusively in underweight patients.

The molecular mechanism of sarcopenia remains poorly understood. Skeletal muscle was recently identified as an endocrine organ[28]. It has therefore been suggested that cytokines and other peptides are produced, expressed and released by muscle fibres. For example, interleukin (IL) 6 is released from skeletal muscle[28], which may subsequently affect liver metabolism. Both the level and timing of IL-6 release appear to be determining factors for the biological effect in patients with liver fibrosis and HCC[28]. Furthermore, levels of insulin-like growth factor (IGF) 1, which plays a stimulatory role in the development and regulation of skeletal muscle mass[28], are decreased in patients with sarcopenia. In some reports, serum IGF-1 levels were significantly lower in patients with cirrhosis than in healthy subjects, and were correlated with the degree of liver dysfunction. Low serum IGF-1 levels were significantly correlated with advanced clinicopathological parameters, and indicative of poor overall survival in HCC[29]. IGF-1 is produced mainly by the liver, and it may be that serum IGF-1 levels are lower in patients with sarcopenia and that low IGF-1 levels promote the progression of HCC. Further study is needed to clarify the molecular mechanism concerning muscle–liver cross-talk.

It is important to note that, among the significant prognostic factors for overall survival, skeletal muscle mass can be evaluated before hepatectomy. Similarly, skeletal muscle mass, ICGR15, serum DCP level and stage can be evaluated before hepatectomy to prognosticate recurrence-free survival. The identification of patients with sarcopenia before hepatectomy might permit early

preventive strategies to maintain muscle mass, in order to improve prognosis and patient selection for hepatectomy. A recent study indicated that a late evening snack, as an intervention to reduce the fasting phase in patients with cirrhosis, has the potential to improve skeletal muscle proteolysis[30].

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Operative details in patients with hepatocellular carcinoma with, and without sarcopenia (Word document)

Snapshot quiz

Snapshot quiz 13/36

Answer: The computed tomography angiogram shows a large right popliteal aneurysm. The options for management are: radiological stenting using a covered stent; and a bypass procedure to exclude the aneurysm. The patient was managed with a bypass procedure from the superficial femoral artery to the below-knee popliteal artery using reversed saphenous vein. The aneurysm was ligated proximally and distally. This aneurysm was deemed unsuitable for radiological stenting owing to the tortuosity of the vessel. The right leg was swollen due to thrombosis of the popliteal vein caused by the pressure effect from the popliteal aneurysm. As this was at least 6 weeks old, the patient did not receive warfarin therapy.

Third or more repeat hepatectomy for recurrent hepatocellular carcinoma

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Background. *We sought to evaluate the surgical results of third or more repeat hepatectomy for recurrent hepatocellular carcinoma (HCC). The role of repeat hepatectomy for recurrent HCC, especially in cases with third or more repeat hepatectomy, is controversial.*
Methods. *We performed A retrospective, cohort study to analyze the surgical results of repeat hepatectomy performed at a single medical center from 1989 to 2011. A total of 1,000 hepatectomies for HCC were divided into 3 groups: A first hepatectomy group (n = 791), second hepatectomy group (n = 163), and third or more hepatectomy group (n = 46). Operative results and patient prognoses were compared among the 3 groups.*
Results. *There were no differences in early surgical results such as mortality and morbidity among the 3 groups. The 5-year survival rates after the first, second, and third or more hepatectomy were 67%, 60%, and 43%, respectively (P = .1913). There was a significant difference in disease-free survival among the 3 groups, and the 5-year disease-free survival rates after first, second, and third or more hepatectomy were 37%, 29%, and 18%, respectively (P = .0169).*
Conclusion. *Third or more repeat hepatectomy for recurrent HCC was performed safely and associated with relatively long-term survival. Third or more repeat hepatectomy for recurrent HCC seems justified, but high rate of HCC recurrence remains a problem. (Surgery 2013;154:1038-45.)*

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HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common malignancy worldwide, with an annual occurrence of ≥1 million new cases, and is responsible for 500,000 deaths worldwide every year.[1,2] The mainstay of curative treatment for HCC is hepatectomy. With advances in operative techniques and perioperative care,[3,4] the results of hepatectomy for HCC have greatly improved. Nonetheless, the long-term survival after hepatectomy remains unsatisfactory because of the high incidence of intrahepatic recurrence in up to 68–98% of patients.[5] Thus, effective therapeutic strategies for intrahepatic recurrence are critical to prolonging survival after hepatectomy for HCC. In the past 2 decades, repeat hepatectomy has been reported to be safe and to prolong survival after intrahepatic recurrence.[6-14] Recently, salvage liver transplantation was proposed as a curative option for intrahepatic recurrence of HCC, but it is still not widely used because of the insufficient numbers of cadaveric donors and limited availability of appropriate living donors.[15-17] Moreover, the problem of further HCC recurrence after repeat hepatectomy or liver transplantation is adovocated.[17,18] For second recurrence of colorectal liver metastases, third hepatectomy has been reported to be beneficial.[19] However, there have been few reports on further hepatectomy for a second or third recurrence of HCC.[8,10,13,14,20]

Our department has aggressively adopted repeat hepatectomy as the main curative option for treating recurrent HCC, irrespective of the number of recurrences. A retrospective review of patients undergoing hepatectomy for primary and recurrent HCC over 20 years in a single institution was conducted in order to clarify the role of repeat hepatectomy, especially third or more hepatectomy, for recurrent HCC.

METHODS

Patients. A total of 1,000 hepatectomies for HCC were performed at the Department of Surgery, Hiroshima Red Cross and Atomic Bomb

Accepted for publication April 19, 2013.

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0039-6060/$ - see front matter

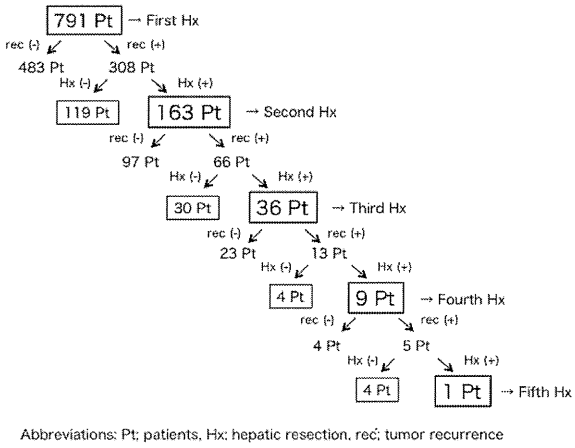
http://dx.doi.org/10.1016/j.surg.2013.04.046

Survivors Hospital, between January 1989 and March 2010. A flow diagram showing the treatment and outcome of this cohort is provided in Fig 1. Repeat hepatectomy was performed in 209 patients, and consists of a second hepatectomy in 163 patients, third hepatectomy in 36, fourth hepatectomy in 9, and fifth hepatectomy in 1. This series was divided into 3 groups: First hepatectomy (n = 791), second hepatectomy (n = 163), and third or more hepatectomy (n = 46). The medical records of patients in this series were followed until March 2012, and the median follow-up period was 52 months.

Operative techniques and follow-up methods. The details of the operative techniques and patient selection criteria for repeat hepatectomy have been reported previously, and are almost identical to those of the initial hepatectomy for primary HCC.[6,21,22] Patients with an indocyanine green dye retention rate at 15 minutes of <40% were selected for hepatic resection, and patients with an indocyanine green dye retention rate at 15 minutes of <35% were selected for anatomic resection.[22] In principle, this selection criteria for hepatic resection was consistent even in the third or more hepatectomy group. Anticoagulant drugs, such as nafamostat mesilate,[23] have been given perioperatively since 1996, and preoperative steroid administration has been routinely performed since 2006.[24]

In almost all hepatic resections, intermittent Pringle's maneuvers consisting of clamping the portal triad for 15 minutes and then releasing the clamp for 5-minute intervals or hemivascular occlusions were applied.[25,26] The clump-crushing method was used to transect the liver parenchyma until 2001, a CUSA system (Valley Lab, Boulder, Colo) has been used since 2002, and a VIO soft-coagulation system (ERBE Elektromedizin, Tübingen, Germany) has been added since 2010.[27] An intraoperative bile leakage test has been routinely performed since 2006.[28] Since 2008, a hyaluronic acid-carboxymethylcellulose membrane (Seprafilm, Genzyme Corporation, Cambridge, MA) was inserted around the liver bed to reduce the adhesion of the duodenum, transverse colon, and omentum to the hepatic hilum.[29]

We examined 5 surgical outcomes among 3 groups: Postoperative mortality, morbidity, duration of hospital stay, overall survival, and disease-free survival. Any death that occurred in the hospital after hepatectomy was recorded as a mortality. Complications were evaluated by Clavien's classification[30] of surgical complications, and those with a score of grade ≥II were defined as positive. After discharge, all patients were examined for HCC recurrence by ultrasonography and tumor markers such as α-fetoprotein and des-γ-carboxy prothrombin every month, and by dynamic computed tomography every 3 or 4 months.[31] No patient received adjuvant chemotherapy or adjuvant lipiodolization in our series. We treated recurrent HCC by repeat hepatectomy,[32] ablation therapy,[33] and lipiodolization[34] according to the previously described strategy.[6]



Abbreviations: Pt; patients, Hx; hepatic resection, rec; tumor recurrence

Fig 1. Treatment and outcome flow diagram.

Statistical analysis. Continuous variables were expressed as mean values ± standard deviation and compared using analysis of variance. Categorical variables were compared using either the Chi-square or Fisher's exact test as appropriate. Survival durations were measured from the last time of operation. Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. All analyses were performed with Statview 5.0 software (Abacus Concepts, Berkeley, Calif).

RESULTS

Comparisons of background characteristics among patients undergoing third or more repeat hepatectomy for recurrent HCC. The comparisons of patient characteristics among the 3 groups are summarized in Table I. There were significant differences in patient age (first hepatectomy, 65 ± 10 years; second, 68 ± 10 years; third or more, 71 ± 9 years; $P < .0001$). There were no differences in the positive rate of hepatitis B surface antigen (first, 19%; second, 17%; third or more, 20%; $P = .4027$) or hepatitis C virus antibody (first, 64%; second, 69%; third or more, 61%; $P = .6045$). Patients in the second and the third or more hepatectomy groups maintained liver

Table I. Comparisons of patients' background characteristics

Variables	*First* (n = *791*)	*Second* (n = *163*)	*Third or more* (n = *46*)	P *value*
Age (y)	65 ± 10	68 ± 10	71 ± 9	<.0001
Male/female	544/247	113/50	39/7	.0716
Body mass index	23.0 ± 3.1	22.9 ± 3.1	22.3 ± 2.3	.3118
Diabetes, *n* (%)	224 (28)	42 (26)	13 (28)	.7883
Drinking, *n* (%)	207 (26)	38 (23)	9 (20)	.4027
HBs-Ag+, *n* (%)	148 (19)	29 (17)	9 (20)	.6812
HCV-Ab+, *n* (%)	508 (64)	112 (69)	28 (61)	.6045
Platelets ($\times 10^4/\mu L$)	18.6 ± 38.4	12.8 ± 4.7	13.2 ± 4.4	.1058
Total bilirubin (mg/dL)	0.8 ± 0.4	0.7 ± 0.3	0.7 ± 0.3	.0009
Albumin (g/dL)	3.9 ± 0.4	4.0 ± 0.4	4.0 ± 0.4	.0020
Aspartate aminotransferase (IU/L)	53 ± 35	40 ± 25	35 ± 15	<.0001
Alanine aminotransferase (IU/L)	53 ± 38	40 ± 25	35 ± 15	<.0001
Prothrombin time, *n* (%)	88 ± 16	89 ± 15	91 ± 13	.1649
ICGR-15, *n* (%)	18.5 ± 10.8	19.3 ± 10.5	19.7 ± 8.4	.5119
Child A, *n* (%)	734 (93)	156 (96)	45 (98)	.5089

Ab, Antibody; *HbS-Ag*, hepatitis B surface antigen; *HCV*, hepatitis C virus; *ICGR-15*, indocyanine green dye retention rate at 15 minutes.

function better and had lower total bilirubin levels than those in the first hepatectomy group (first, 0.8 ± 0.4 mg/dL; second, 0.7 ± 0.3 mg/dL; third or more, 0.7 ± 0.3 mg/dL; $P = .0009$), but there were no differences in Child–Pugh classification (first, A in 93%; second, A in 96%; third or more, A in 98%; $P = .5089$).

Comparisons of short-term surgical outcomes of third or more repeat hepatectomy for recurrent HCC. The comparisons of short-term surgical outcomes among the 3 groups are summarized in Table II. The operation time was significantly prolonged in the third or more hepatectomy group (first, 225 ± 98 minutes; second, 232 ± 103 minutes; third or more, 267 ± 86 minutes; $P = .0147$). In the repeat hepatectomy groups, the extent of hepatectomy, such as the resected liver volume (first, 152 ± 214 g; second, 56 ± 61 g; third or more, 47 ± 41 g; $P < .0001$) or positive rate of anatomic resection (first, 41%; second, 21%; third or more, 9%; $P < .0001$) was significantly reduced, and the intraoperative transfusion rate (first, 20%; second, 12%; third or more, 15%; $P = .0376$) was significantly decreased. There were no differences in the hospital mortality rate (first, 1.4%; second, 1.2%; third or more, 0.0%; $P = .7177$), postoperative morbidity rate (first, 31%; second, 26%; third or more, 30%; $P = .4237$), and mean duration of hospital stay (first, 20 ± 16 days; second, 17 ± 20 days; third or more, 16 ± 9 days; $P = .1897$).

Comparisons of tumor-related factors of third or more repeat hepatectomy for recurrent HCC. The comparisons of tumor-related factors among the 3 groups are summarized in Table III. There were significant differences in the tumor diameter (first, 3.3 ± 2.4 cm; second, 2.0 ± 0.9 cm; third or more, 1.8 ± 1.0 cm; $P < .0001$) and the number of tumor (first, 1.3 ± 0.8; second, 1.5 ± 1.3; third or more, 1.5 ± 0.9; $P = .0208$). The rate of poorly differentiated HCC was significantly decreased in the repeat hepatectomy groups (first, 30%; second, 17%; third or more, 15%; $P = .0002$), but there were no differences in the positive rate of portal venous infiltration ($P = .0721$) or intrahepatic metastasis ($P = .3162$). The positive rate of histologic cirrhosis also showed no significant differences among the 3 groups (first, 53%; second, 60%; third or more, 52%; $P = .9009$).

Survival rate after third or more repeat hepatectomies for recurrent HCC. The overall survival curves after hepatectomy for HCC of the 3 groups are illustrated in Fig 2. There were no differences in overall survival rates, and the 5-year survival rate of the patients who underwent third or more hepatectomy for recurrent HCC reached 43% (first, 67%; second, 60%; $P = .1913$). The disease-free survival curves after hepatectomy for HCC of the 3 groups are illustrated in Fig 3. The disease-free survival rate in the third or more hepatectomy group was significantly decreased, and the 5-year disease-free survival rate of the third or more hepatectomy group remains quite low, that is, 18% (first, 37%; second, 29%; $P = .0169$).

The overall survival and disease-free survival rates after second hepatectomy according to the treatment type (third hepatectomy vs. non-hepatectomy) are illustrated in Fig 4. The overall survival rate is significantly better in the third hepatectomy group, and the 5-year survival rate

Table II. Comparisons of surgical outcomes

Variables	*First* (n = *791*)	*Second* (n = *163*)	*Third or more* (n = *46*)	P *value*
Surgical outcomes				
Operation time (min)	225 ± 98	232 ± 103	267 ± 86	.0147
Blood loss (g)	681 ± 1062	627 ± 805	764 ± 797	.6873
Resected volume (g)	152 ± 214	56 ± 61	47 ± 41	<.0001
Transfusion (%)	159 (20)	19 (12)	7 (15)	.0376
Hr 0:S:1-2	468:129:79	129:14:4	42:2:0	<.0001
Anatomic resection, *n* (%)	323 (41)	34 (21)	4 (9)	<.0001
sm (mm)	4.6 ± 6.2	3.1 ± 3.9	2.4 ± 3.2	.0013
Postoperative courses				
Mortality, *n* (%)	11 (1.4)	2 (1.2)	0 (0.0)	.7177
Morbidity, *n* (%)	243 (31)	42 (26)	14 (30)	.4237
Hospital stay (d)	20 ± 16	17 ± 20	16 ± 9	.1897

Hr 0, Limited resection; *Hr S*, subsegmentectomy; *Hr 1*, segmentectomy; *Hr 2*, bi-segmentectomy; *sm*, surgical margin.

Table III. Comparisons of tumor-related factors

Variables	*First* (n = *791*)	*Second* (n = *163*)	*Third or more* (n = *46*)	P *value*
Tumor diameter (cm)	3.3 ± 2.4	2.0 ± 0.9	1.8 ± 1.0	<.0001
Tumor number	1.3 ± 0.8	1.5 ± 1.3	1.5 ± 0.9	.0208
Poorly dif. (%)	239 (30)	27 (17)	7 (15)	.0002
fc+, *n* (%)	514 (65)	86 (53)	21 (46)	.0015
fc-inf+, *n* (%)	404 (51)	67 (41)	20 (43)	.0165
vp, *n* (%)	436 (55)	96 (59)	28 (60)	.0721
im, *n* (%)	105 (13)	18 (11)	3 (7)	.3162
Stage III or IVA, *n* (%)	93 (12)	68 (42)	16 (35)	.0507
α-Fetoprotein (ng/mL)	14 ± 164	28 ± 102	18 ± 29	.6010
Des-γ-carboxy prothrombin (mAU/mL)	37 ± 57	20 ± 50	15 ± 52	.9009
lc+, *n* (%)	420 (53)	98 (60)	24 (52)	.2462

dif, Differentiation; *fc*, fibrous capsule; *fc-inf*, fibrous capsule infiltration; *vp*, portal venous infiltration; *im*, intrahepatic metastasis; *lc*, liver cirrhosis.

of the non-hepatectomy group remains low (17%). The disease-free survival rate is significantly better in the third hepatectomy group, and the 2-year disease-free survival rate of the non-hepatectomy group remains low (21%). As for the fourth or fifth hepatectomy, 6 of 10 patients (60%) survived >2 years without recurrence, and all patients survived during this follow-up period. However, 11 of 14 patients (79%) with non-hepatectomy treatment for third recurrence or more had early recurrence and 5 of these patients (36%) died within 2 years.

DISCUSSION

This study comprised a longitudinal observation of surgical results of repeat hepatectomies for recurrent HCC in the largest patient group yet reported, and using a nearly constant strategy over 20 years. Hepatectomy remains as the main option for HCC treatment,[1,2] and repeat hepatectomy for recurrent HCC was first reported to be effective >2 decades ago.[6-14] Hepatectomy remains a complex operative procedure with inherent complications.[3-5] Of course, the more often hepatectomy is repeated, the more difficult the procedures becomes owing to the intra-abdominal adhesions caused by previous hepatectomy. This was also true in our series, in which the mean operation time was significantly prolonged in the third or more hepatectomy group (first, 225 ± 98 minutes; second, 232 ± 103 minutes; and third or more, 267 ± 86 minutes; $P = .0147$). However, we also found there were no differences in early surgical results, such as mortality, morbidity, and the mean duration of hospital stay, among the 3 groups. As for the third or more hepatectomy group, the mortality rate was zero and the mean duration of hospital stay was shortened to 16 days in our series. With meticulous operative procedures and perioperative managements for repeat hepatectomies, third or more hepatectomy for recurrent HCC could be safely performed.[13,20]

Comparing surgical outcomes, the extent of hepatectomy was reduced in the repeat hepatectomy groups. This may have been owing to the smaller tumor diameter in the repeat hepatectomy groups (first, 3.3 ± 2.4 cm; second, 2.0 ± 0.9 cm;

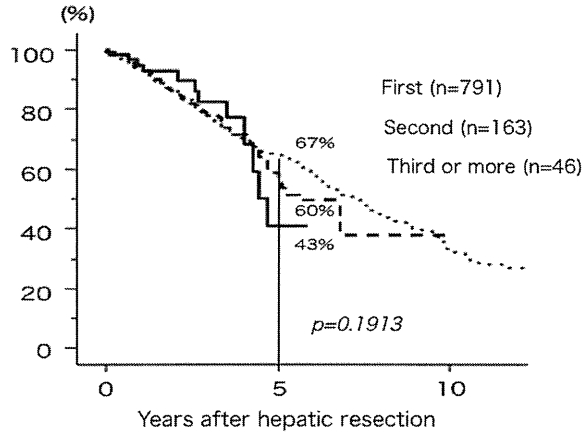


Fig 2. Overall survival curves of patients with first hepatectomy for primary hepatocellular carcinoma (HCC), second hepatectomy for recurrent HCC, and third or more hepatectomy for re-recurrent HCC are illustrated. There were no differences between the 3 groups, and the 5-year survival rates were 67% in the first hepatectomy group, 60% in the second hepatectomy group, and 43% in the third or more hepatectomy group is 43% ($P = .1913$).

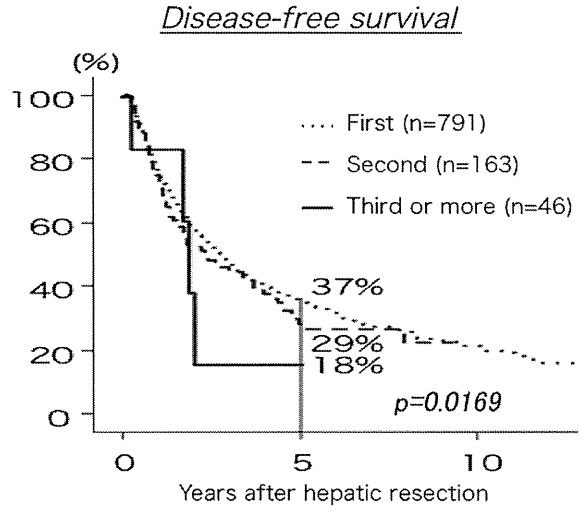


Fig 3. Disease-free survival curves of patients with first hepatectomy for primary hepatocellular carcinoma (HCC), second hepatectomy for recurrent HCC, and third or more hepatectomy for re-recurrent HCC are illustrated. Disease-free survival is significantly worse in the third or more hepatectomy group, and the 5-year disease-free survival rates were 37% in the first hepatectomy group, 29% in the second hepatectomy group, and 18% in the third or more hepatectomy group ($P = .0169$).

third or more, 1.8 ± 1.0 cm; $P < .0001$). It is not surprising that the size of HCC removed by repeat hepatectomy was smaller than that removed by first hepatectomy, because most of the tumors were identified during routine follow-up when asymptomatic. Tumor size in HCC is considered to be the most reliable factor for predicting the degree of malignancy,[35] and HCC of ≤2 cm in diameter has low-grade malignancy based on the so-called "stepwise progression" hypothesis.[36] This smaller diameter would help to reduce the surgical stress during third or more hepatectomy for recurrent HCC, and thus was likely among the factors contributing to the good short-term postoperative results. In addition, according to the patient background in Table I, patients with repeat hepatectomies showed a better preservation of liver function. We previously reported that liver dysfunction was a predictive factor linked to postoperative mortality and morbidity.[3,22] The improvements of short-term postoperative results in the repeat hepatectomy groups for recurrent HCC are attributable to the adequate selection of surgical candidates for recurrent HCC.

The overall survival rates of the patients who underwent third or more hepatectomy for recurrent HCC were relatively good, and the 5-year survival rate reached 43% in our series (first, 67%; second, 60%; $P = .1913$). However, the disease-free survival of patients with third or more hepatectomy was significantly shorter than those in the other groups, and the 5-year disease-free survival rate of patients with third or more hepatectomy remains quite low, at 18% (first, 37%; second, 29%; $P = .0169$). Wu et al[20] reported that the more often a repeat hepatectomy for recurrent HCC was performed in an individual patient, the shorter the disease-free interval was thereafter. Irrespective of the high rate of recurrence of HCC in patients with third or more hepatectomy, the overall survival was relatively maintained. Patients with third or more hepatectomy showed a better preservation of liver function (Table I). Patients with good liver function could receive more aggressive and curative treatment for recurrent HCC,[15-17] and this was among the causes of the maintenance of relatively long-term overall survival in patients with third or more hepatectomy for recurrent HCC. On the other hand, there have been several reports in which transfusion was related to the poor prognosis of patients with HCC after hepatectomy.[37-39] The reduced transfusion rate in patients with third or more hepatectomy in our series would also be among the causes for the maintenance of good overall survival in patients with third or more hepatectomy for recurrent HCC.

HCC recurrence is mainly owing to micrometastases or multicentric recurrence.[40,41] In the present series, according to the Kaplan–Meier

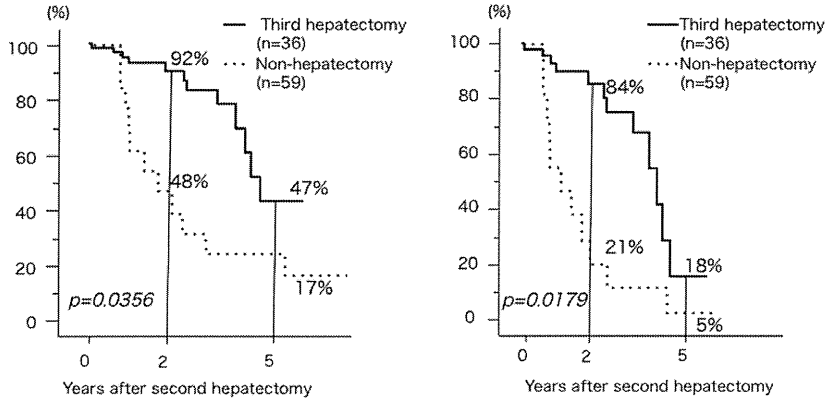


Fig 4. Overall and disease-free survivals after second hepatectomy according to treatment type are shown: third hepatectomy versus non-hepatectomy. The overall survival rate is significantly better in the third hepatectomy group, and the 5-year survival rate in the non-hepatectomy group remains low (17%). The disease-free survival rate is significantly better in the third hepatectomy group, and the 2-year disease-free survival rate in the non-hepatectomy group remains low (21%).

curve of disease-free survival in the third or more hepatectomy group, the recurrence after 2 years was drastically increased. Therefore, the remnant liver of patients with third or more hepatectomy for recurrent HCC would have high risk for multicentric recurrence, and preventative measures such as interferon therapy for patients after repeat hepatectomies with chronic hepatitis C would be important.[9] In addition, because of the high rate of recurrence, salvage liver transplantation would be among the treatment choices for recurrence after third or more hepatectomy. However, the drawbacks of liver transplantation include insufficient numbers of cadaveric donors, a lack of appropriate living donors, relatively high mortality of recipients, mortality and morbidity of the living donors, and need for lifelong immunosuppressant therapy and high cost.[15-17,42] In addition, Ng et al[16] reported that the long-term results of nontransplant therapy (5-year survival, 41.8%) and that of liver transplantation (5-year survival, 54%) for transplantable HCC are similar.[16]

With respect to second recurrence, Fig 4 indicates that the overall and disease-free survival rates of patients who underwent third hepatectomy were significantly better than those of patients with non-hepatectomy treatment. But it cannot be concluded definitively that third hepatectomy is superior to other modalities for the treatment of second recurrence of HCC. Comparison of the prognosis after repeat hepatectomy versus other treatments may not be valid because radiofrequency ablation (RFA) or other therapies would be offered to patients on a selection bias. Patients who did not undergo repeat hepatectomy may have had poorer liver functional reserve and/or too advanced recurrent HCC. Chan et al[33] reported that there were no differences in survival between patients with repeat hepatectomy and those with RFA. However, in the same report the 5-year overall and disease-free survival after second hepatectomy for recurrent HCC were fairly low, that is, 35% and 24%, respectively. These data were worse than ours (5-year overall, 60%; 5-year disease-free, 29%). Pathologic examination of totally explanted liver after RFA for HCC showed that complete tumor necrosis rarely occurred (47%) after RFA.[43] To compare the survival impacts of repeat hepatectomy with other treatment modalities such as RFA, a prospective, randomized trial of repeat hepatectomy is needed.

In conclusion, irrespective of the high rate of recurrence, third or more repeat hepatectomy for recurrent HCC was justified, and was performed safely and associated with relatively long-term survival.

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