developed provides real-time visualizations and interactive control according to user requirements during surgical simulation procedures.

Methods

Patients

Seven patients (three with hepatocellular carcinoma, three with liver metastases from colorectal cancer, and one living-related liver donor), who were scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between March 2009 and November 2011, were screened for this study. All patients gave written informed consent for participation in this study, and the protocol was approved by the institutional ethics committee.

Development of the Liver Surgery Visualization and Simulation System

Our surgical simulation system development consisted of three stages: liver segmentation, vessel extraction, and surgical visualization and simulation (Fig. 1). First, we segmented the liver from the CT volume data using our previously published approach.[1] Next, we extracted hepatic vessels in three CT imaging phases using a multi-scale filter.[2] Finally, the segmented liver and extracted vessels were rendered in the visualization system for use in surgical planning simulations.

Liver Segmentation

Liver segmentation started with preprocessing, which included eliminating noise, defining the region of interest to reduce image size and to increase the speed of the code, removing some non-hepatic tissues, and manual segmentation of the liver in a large slice. The liver's location inside the ribs allowed us to remove the muscles between and behind the ribs, whose intensity range overlapped with hepatic tissue. Starting from the mask of the liver obtained from manually segmented slices, we employed a Gaussian mixture model with two components ($G(\mu_i, \sigma_i|\pi_i), 1 \leq i \leq 2$) to model the intensity distribution of liver and tumors. We employed the EM algorithm[1] to find statistical parameters of the mixture model. For each mode i of the mixture model, we thresholded new slices in the region $[\mu_i - \beta\sigma_i, \mu_i + \beta\sigma_i]$ to find liver candidate pixels, where $0 < \beta < 1$ is a real number. k-means clustering was employed to reject non-liver pixels and retain liver index pixels. We then thresholded the original image in the whole range of each mode i ($[\mu_i - 3\sigma_i, \mu_i + 3\sigma_i]$) to include more pixels. We assigned to the new pixels a probability $p(x) = 1/d(x)$, where $d(x)$ is the Hausdorff distance of a pixel from the index pixels.[3] In this way, we established a liver probability map. We thresholded the map to find the liver boundaries, which we smoothed using Fourier transform. In the final step of the liver segmentation algorithm, the initial liver surface was used as the input for a 3D geodesic active contour.[4] A few iterations of the active contour algorithm were needed to achieve the final result.

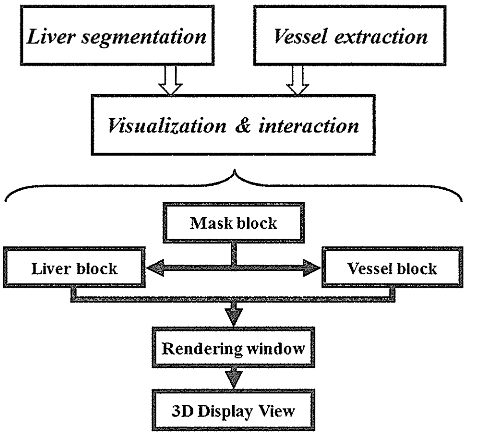

Fig. 1 Flow chart of our liver surgery visualization and simulation system

Vessel Extraction

Vessel information is very important for surgical simulations and is a key surgical consideration. In the vessel extraction and enhancement module, the hepatic artery, portal vein, and hepatic vein were extracted from arterial, portal venous, and delayed phases, respectively. The origins of these vessels were usually outside of the liver mask. We added the origins to the vascular structures during enhancement and then trimmed the results.

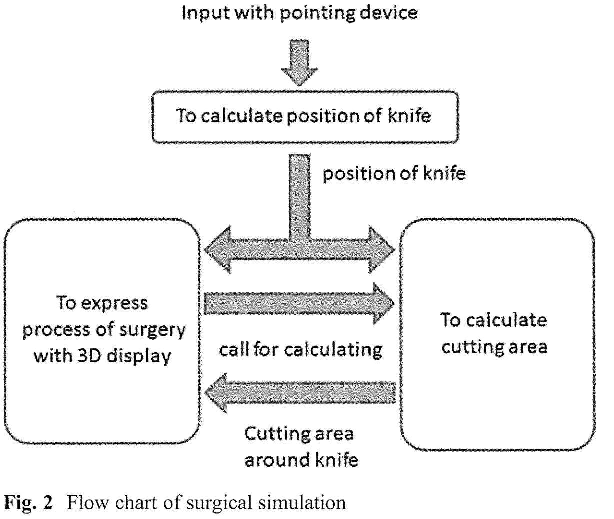

Fig. 2 Flow chart of surgical simulation

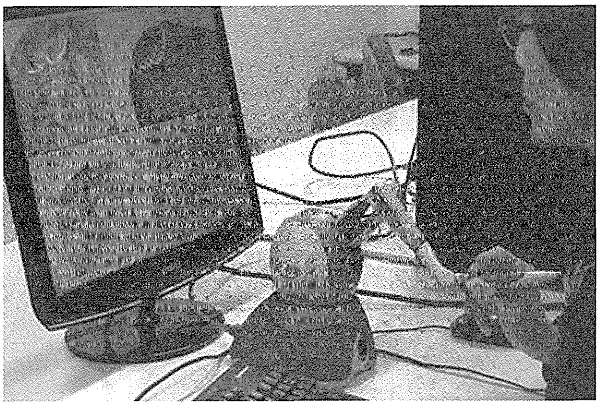

Fig. 3 The surgical simulation system and its screens

The segmented livers were used as masks for vessel extraction. To extract hepatic vessels, we employed the Frangi method, which is a Hessian-based approach to tubular structure enhancement.[2] This method was built on the basis that local image structures are inherent in the Hessian matrix of image voxels. Eigenvalues of the Hessian matrix reveal image structures, and eigenvectors show the main directions into which the local secondary structures of the image can be divided.

3D Visualization

Almost all medical visualization systems to date have used the Visualizing Tool Kit (VTK) library.[6] However, VTK is only used for CPU processing and its processing time is long, making it unsuitable for an interactive surgical simulation system. To accelerate the speed of visualization and interaction, we developed an original visualization library based on GPU (graphics processing unit) computing.[7, 8] We segmented the liver region and modeled the vessel surfaces in the following five steps. First, the segmented liver and extracted vessels were read and then re-sampled using a shrinkage factor to increase the speed of the application. Next, the contour was extracted for surface rendering. To cut a part of the liver, a clipping filter was used that simultaneously prepared several masking patterns and removed parts of the liver or vessels. Finally, a smoothing filter was applied to the extracted surface, and the result was sent to the mask block. The mask block aligned the liver and the vessel models in the same virtual space and displayed them together to guide doctors during liver sectioning.

Interactive Surgical System

We aimed not only to visualize the liver and vessel model but also to simulate an interactive surgical procedure, in which a liver was sectioned according to the visualization information. Our surgical simulation system consisted of three elements: the position of the virtual scalpel, the re-rendered liver modeling, and the determination of the cutting region (Fig. 2).

In a surgical simulation system, the input device is expected to replicate the movements of a real scalpel. Since it was impossible to control the input position of the virtual blade accurately using conventional input devices such as a keyboard and mouse, our system used a pen-like haptic 3D pointing device (Phantom Omni haptic device) to simulate a scalpel.[11] The Omni haptic pointing device had high fidelity force feedback to sense motion in six degrees of freedom, making it possible to touch and manipulate virtual objects in all axes.[11] The position of the device tip reflected the blade position in virtual space. The cutting position in virtual space was calculated using the input position of the virtual scalpel

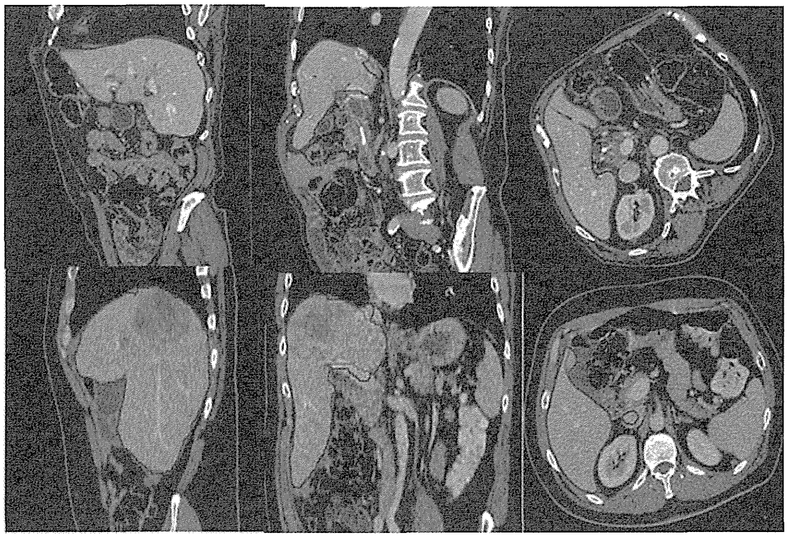

Fig. 4 Liver segmentation. The outline of the standard reference segmentation is in *red*; the outline of the segmentation obtained using the method described in this paper is in *blue*. Slices are displayed with a window width of 400 and a level of 70

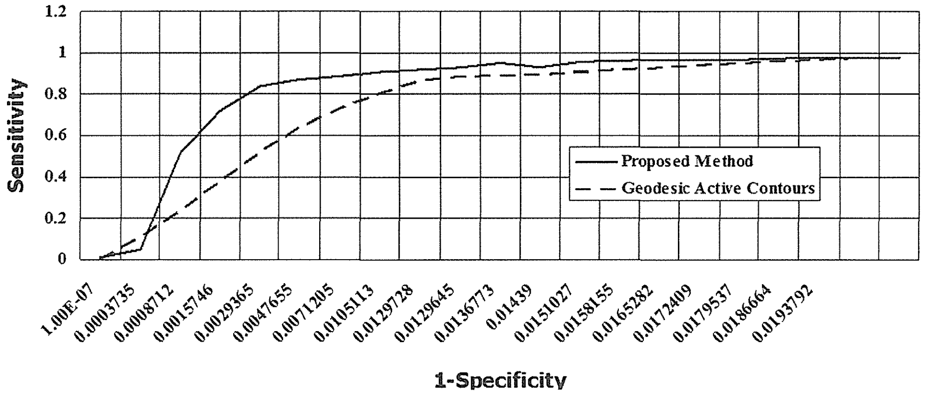

Fig. 5 Comparison of ROC curves. ROC curves comparing the results of the liver segmentation by our method and the geodesic active contour method

(the 3D pointing device), represented by a green ball in real time. The user (surgeon) could easily move the virtual scalpel to the desired position by looking at the 3D liver model, as shown in Fig. 3. The cutting or deformation region was controlled by changing the pressure applied to the 3D pointing device. The post-incision liver surface was smoothly re-rendered. Depending on the surgeon's experience, a region smaller than the desired region was usually initially selected for cutting, and the process was repeated several times until complete removal. In addition, there was tactile feedback when the stylus (scalpel) touched a virtual object.

We used a 3D display in our system. The 3D display had a refresh rate of 120 Hz and showed a 3D structure. Using the 3D display, the vessels' relative position was easily assessed for accurate surgical simulation. Our system consisted of four screens (Fig. 3). The right two windows were main screens reflecting the position of the virtual scalpel blade relative to the liver model. The upper right screen showed the opaque liver, while the lower right window showed the transparent version with visible vessels. The left two windows were assistance screens showing details of the locally visible liver and vessels or of the global vessels from different angles.

Our surgical simulation system on a computer has the following specifications: graphics board (GeForce 8700M GT, 1.52 GB, NVidia, Santa Clara, CA), CPU (Intel Core i7-2600, 3.40 GHz~3.9 GHz, Intel Corp., Santa Clara, CA), GPU (Quadro 4000, NVidia), memory (8.00 GB), and 3D display (SyncMaster 2233RZ, Samsung, South Korea).

Results

Liver Segmentation

Two typical liver segmentation results are shown in Fig. 4. The outline of the reference (manual segmentation results of liver specialists) and the proposed method segmentation results are shown in red and blue, respectively. Our proposed method achieved good segmentation results.[4] The comparison

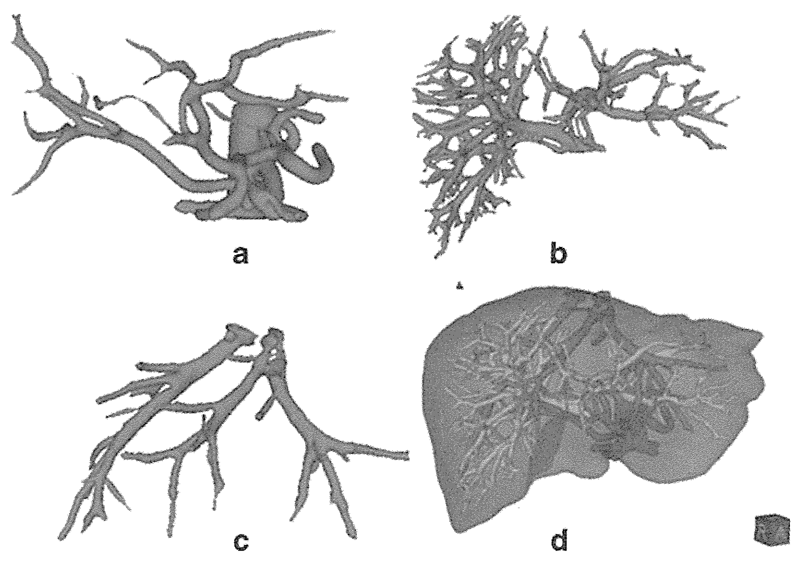

Fig. 6 Iso-surface visualization of the liver and its vascular structure. **a** Hepatic artery. **b** portal vein. **c** hepatic vein. **d** liver and its vascular structure. In **d**, the hepatic artery, portal vein, and hepatic vein are colored in *red*, *yellow*, and *blue*, respectively

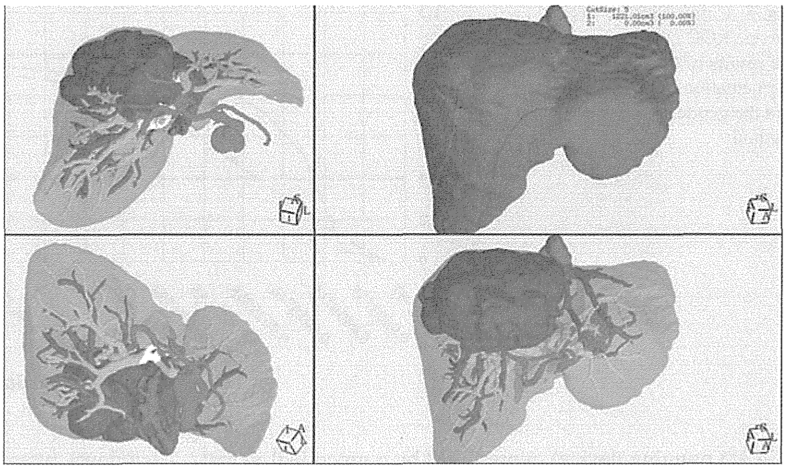

Fig. 7 Surgical simulation results. A case of right trisectionectomy for hepatocellular carcinoma. Artery (*red*), portal vein (*yellow*), hepatic vein (*blue*), and hepatocellular carcinoma (*dark brown*)

of the ROC curves of our proposed method and the conventional geodesic active contour (GAC) method is shown in Fig. 5.

Vessel Extraction and Visualization

Figure 6 shows extracted hepatic vessels. The hepatic artery was extracted from the first phase, the portal vein was extracted from the second phase, and the hepatic veins were usually extracted from the third phase datasets. In Fig. 6d, the liver is shown with its vascular structure.

Surgical Simulation Results

Figure 7 shows the simulation of right trisectionectomy in hepatocellular carcinoma. The liver parenchymal dissection was manually extracted from a CT image under a surgeon's guidance and was modeled for visualization together with the liver and vessels. First, the surgeon dissected the right hepatic artery, exposing the right portal vein, which was then circumferentially mobilized by cutting the small posterior branches to the caudate lobe. The right portal vein was divided (Fig. 8). All vessels entering the lateral segment were divided during parenchymal transection (Fig. 9). After completion of the parenchymal transection and exposure of the right and middle hepatic veins, these vessels were divided (Fig. 10).

Discussion

To date, many surgical simulators have been developed,[9] most for education and training, using a general anatomic model. These systems were not developed as disease-oriented or individual patient-oriented simulators. MeVis Medical Solutions (Bremen, Germany) has developed disease-oriented software products for clinically relevant problems in image-based medicine and has been a world leader in these research fields.[10] One of the MeVis medical software products is liver and hepatic vascular visualization for patient-oriented surgical planning. Though liver and vascular visualization is very useful for presurgical planning, it

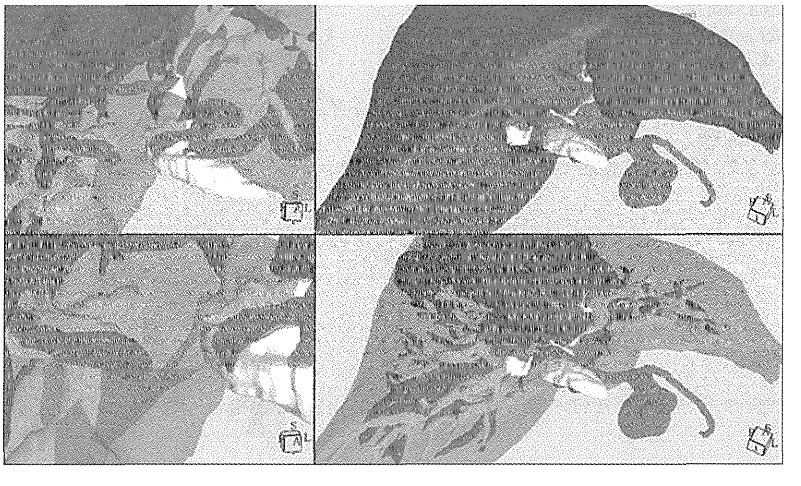

Fig. 8 Surgical simulation in the hilar portion. Right hepatic artery (*red*) and portal vein (*yellow*) were divided in the extrahepatic hilar portion

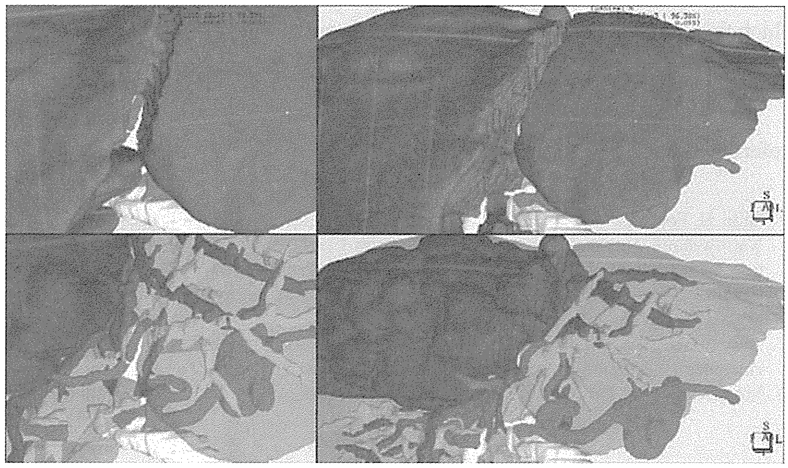

Fig. 9 Surgical simulation of liver parenchymal dissection

is difficult for interns or medical students to plan using the visualization alone. The main contribution of our system is that we not only visualized the liver structure but also constructed a simulator with the patient's particular hepatic anatomy. Using our system, surgeons can perform patient-oriented or disease-oriented surgical simulations and training to improve surgical accuracy and workflow efficiency. Surgeons can determine the optimal approach in advance and can easily check excision margins.

We used a novel image processing technique for accurate semi-automatic liver segmentation. Segmentation accuracy was estimated to be greater than 90 %, and the processing time for liver segmentation from CT volume was only thirty seconds, which is very efficient, compared with conventional manual liver segmentation. The comparison of the ROC curves of our proposed method and the conventional GAC method[4] is shown in Fig. 5. The segmentation accuracy of our proposed method was much higher than that of the conventional GAC method. The extraction accuracy of vessels by multi-scale filters was also greater than 90 %.

Since our system used 3D devices (3D display and 3D pointing device), it was very easy to simulate an interactive surgery. In a 3D display, the relative position of the vessels was easily determined for the simulation. The 3D pointing device, which is similar to a pen, simulated the scalpel, and the position of its tip reflected the scalpel blade position in virtual space. In addition, the pressure applied to the 3D pointing device was automatically estimated, to determine the deformation or cutting region. Three liver surgeons evaluated our system and agreed that it provided an easily operated simulation using individual patient data (liver, tumor, and vessels).

In conclusion, there is a high demand for surgical assistance systems to assess individual patients. We developed a system in which the hepatic vessels were semi-automatically extracted from the segmented liver images, and the 3D shape of the liver and extracted vessel distribution were visualized using a surgical simulation system. The 3D visualization demonstrated details of individual liver structure, resulting in better understanding and practical surgical simulation. Though our system is currently only for surgical simulations, we have plans to expand it to a surgical navigation system, in

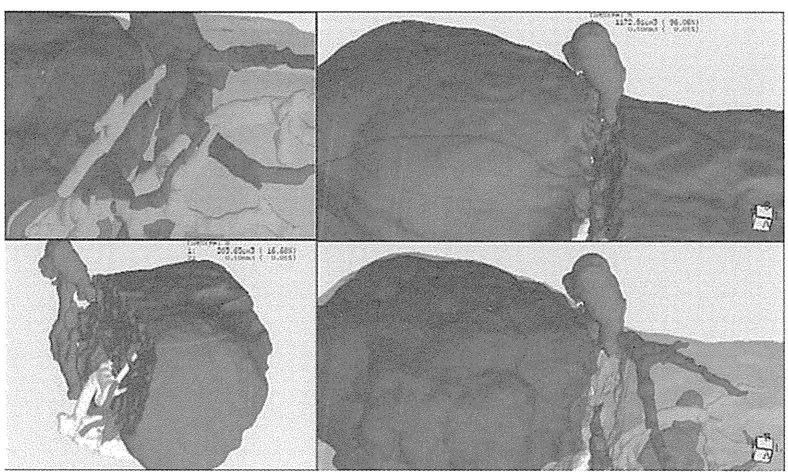

Fig. 10 Surgical simulation after division of the hepatic vein. Right and left hepatic veins (*blue*) were divided in the extrahepatic portion

which the 3D liver model will be registered to a real liver in real time.

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Clinical Science

Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy

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KEYWORDS:
Liver cancer;
Cirrhosis;
Hepatectomy;
Exercise;
Insulin resistance

Abstract

BACKGROUND: The aim of this study was to examine the outcomes of exercise therapy in patients with hepatocellular carcinoma who underwent hepatectomy.

METHODS: Fifty-one patients with hepatocellular carcinoma were randomized to diet therapy alone (n = 25) or to exercise in addition to diet therapy (n = 26). Exercise at the anaerobic threshold of each patient was started 1 month preoperatively, resumed from 1 week postoperatively, and continued for 6 months.

RESULTS: Whole body mass and fat mass in the exercise group compared with the diet group were significantly decreased at 6 months postoperatively. Fasting serum insulin and the homeostasis model assessment score were also significantly decreased. At 6 months, anaerobic threshold and peak oxygen consumption were significantly increased, while serum insulin and insulin resistance were significantly improved in a high-frequency exercise subgroup compared with a low-frequency group.

CONCLUSIONS: Perioperative exercise therapy for patients with hepatocellular carcinoma with liver dysfunction may improve insulin resistance associated with hepatic impairment and suggests a benefit to the early resumption of daily exercise after hepatectomy.

Interest in the role of physical activity in the primary prevention of cancer is increasing as evidence of a protective effect accumulates. Recent reviews of physical activity in relation to cancers such as colon cancer,[1] breast cancer,[2–4] prostate cancer,[5] and all cancers[6–12] have provided a detailed assessment of the level of epidemiologic evidence for the putative association. In Japan, a westernized lifestyle has become common in recent years, and the rates of obesity, diabetes, dyslipidemia, and hypertension have gradually increased. Metabolic syndrome is characterized by insulin resistance and is associated with atherosclerosis and hypertension, as is also recognized as an inflammatory condition.[13,14] Accumulating evidence suggests that insulin resistance plays a key role in both hepatocellular damage and hepatocarcinogenesis by inducing oxidative stress in patients with various liver diseases, including viral infection and fatty liver.[15–17] Because the liver is a major target organ for insulin when regulating the blood glucose level, >70% of patients with liver cirrhosis also exhibit insulin resistance regardless of the etiology.[18]

Management of insulin resistance is a critical issue for patients with chronic liver disease in terms of both

The authors declare no conflicts of interest.

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maintaining liver function and preventing hepatocarcinogenesis. Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide.[19] It is important to maintain good perioperative nutrition and metabolism to improve the prognosis of patients with HCC undergoing hepatectomy.[20,21] So far, little attention has been paid to the role of exercise in the management of hepatectomy patients. In the present study, we aimed to clarify whether a perioperative and postoperative exercise program had any metabolic or physical advantages for cirrhosis patients with HCC who underwent hepatectomy.

Methods

Patients

Patients with HCC who had chronic hepatitis or cirrhosis and were scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between December 2008 and February 2010 were screened for this study. The eligibility criteria for inclusion were as follows: (1) elective hepatectomy, but no bilioenterostomy; (2) age 20 to 80 years; (3) a preoperative diagnosis of HCC with no previous treatment; (4) no other malignancies; (5) Child-Pugh score A or B; (6) adequate cardiopulmonary function (results of electrocardiography, echocardiography, and spirometry within the normal range); (7) leukocyte count $\geq$3,000/mm^3; (8) hemoglobin level $\geq$9.5 g/dl; (9) platelet count $\geq$50,000/mm^3; (10) serum creatinine $<$1.2 mg/dL; (11) total bilirubin $<$2.0 mg/dL; (12) local nodular disease without extrahepatic metastasis; and (13) Eastern Cooperative Oncology Group performance status 0 or 1.[22] Exclusion criteria were inability to perform exercise, ischemic cardiomyopathy, 3rd-degree atrioventricular block, severe obstructive pulmonary disease, and severe hypertension (blood pressure $>$180/110 mm Hg). All patients gave written informed consent for participation in this study, and the protocol was approved by the institutional ethics committee.

The study protocol was explained to all patients, and they understood that they would be randomly assigned to either conventional perioperative management with diet alone (diet group, n = 26) or would receive exercise combined with diet (exercise group, n = 25). The protocol for this study was approved by the institutional ethics committee.

In a preliminary study, we examined the changes in portal blood flow (PBF) with exercise. The pre-exercise and postexercise PBF rate and volume were measured using Doppler ultrasound in healthy age-matched volunteers and patients with HCC with chronic hepatitis or cirrhosis (at 1 month after surgery) using the Ascendus Ultrasound System (Hitachi Aloka Medical, Ltd, Tokyo, Japan), equipped with a multifrequency (2 to 5 MHz) convex transducer. Exercise was performed at the anaerobic threshold (AT) for 20 minutes on a bicycle ergometer, and measurements were obtained before exercise, immediately afterward, and 1 hour after the completion of exercise. In the healthy volunteers, data were also measured at one-third the respiratory compensation point.

Exercise program

Before starting exercise therapy, patients underwent cardiopulmonary exercise testing on a bicycle ergometer using an incremental protocol (5.0, 7.5, and 10 W/min). The 12-lead electrocardiogram was continuously monitored for ST-segment deviation, arrhythmias, and heart rate at rest and during the exercise and recovery periods. Blood pressure was recorded at rest and every 2 minutes during the exercise and recovery periods. Peak oxygen consumption per unit time (Vo_2) was obtained from breath-by-breath analysis of expired air. Peak Vo_2 was defined as the highest mean value during exercise when the subject could no longer continue pedaling at 60 rpm. The AT, the onset of metabolic acidosis, was defined as the break point between carbon dioxide production and Vo_2[23] or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective nadirs before beginning to increase again.[24] Thus, AT was set at the time of maximum fat combustion[25] (Fig. 1). The respiratory compensation point was set at the point at which the ventilatory equivalent for carbon dioxide was lowest before a systemic increase and when the end-tidal carbon dioxide partial pressure reached a maximum and began to decrease.[26] Exercise was stopped when the patient requested it because of fatigue, pain, or headache or if there was a failure to maintain a speed $>$40 rpm for $>$30 seconds despite encouragement.

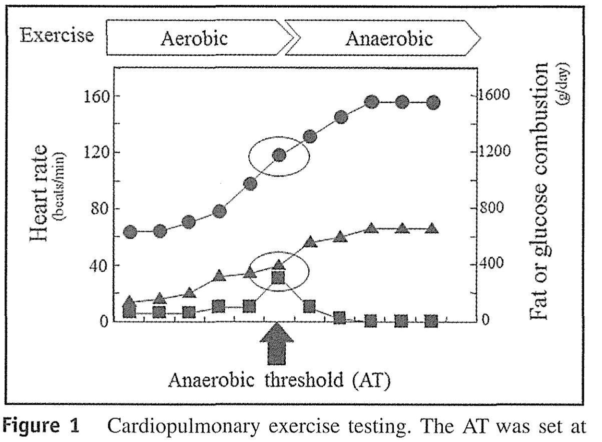

Figure 1 Cardiopulmonary exercise testing. The AT was set at the break point between carbon dioxide production and Vo_2, or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective nadirs before beginning to increase again. Thus, the AT was set at a maximum point of fat combustion. Circles indicate heart rate, triangles indicate glucose combustion, and squares indicate fat combustion.

An exercise program was tailored for each patient. Exercise was started as soon as possible after diagnosis, up to 1 month preoperatively, and was resumed from 1 week postoperatively and continued for 6 months (Fig. 2). The program consisted of 3 60-minute exercise sessions per week. Each session included 5 minutes of stretching exercises, 30 minutes of walking at an intensity based on the AT of each patient, 20 minutes of targeted stretching exercises, and 5 minutes of cooling down with stretching. Once or twice a month postoperatively, a medical doctor and exercise trainer confirmed the frequency and quantity of exercise each patient undertook. Patients in the exercise group showed 2 patterns at 6 months postoperatively, a highly active group and a less active group. We stratified the patients according to the frequency of exercise as standard (3 times a week) or high (5 or 6 times a week).

Diet

Both groups of patients were required to conform to specific diets. The dietitian provided instruction on the specific diet to both groups of patients and checked patient adherence preoperatively and at 1, 3, and 6 months postoperatively. For patients with chronic hepatitis or liver cirrhosis, the daily energy intake was set at 25 to 30 kcal/kg body weight, with a daily protein intake of 1.0 to 1.2 g/kg body weight and a daily sodium chloride intake of 5 to 7 g/kg body weight during the 1-month preoperative and 6-month postoperative periods. For patients with diabetes or fatty livers, daily energy intake was set at 20 to 25 kcal/kg body weight, while the daily sodium chloride intake was set at 6 g/kg body weight for patients with hypertensive.

Laboratory tests and surgery

Before surgery, each patient underwent conventional liver function tests, with measurement of the indocyanine green retention rate at 15 minutes, and ^{99m}Tc-diethylenetriamine penta-acetic acid-galactosyl human serum albumin liver scintigraphy.[27] Hepatitis screening was performed by measurement of hepatitis B surface antigen and hepatitis C antibody. Levels of α-fetoprotein and protein induced by vitamin K absence/antagonism-II were also measured in all patients. Insulin resistance was calculated from the homeostasis model of assessment of insulin resistance (HOMA-IR) using the following formula: HOMA-IR = fasting plasma insulin (μU/mL) $\times$ fasting plasma glucose (mg/dL)/405, which primarily reflects hepatic insulin resistance.[28] Total body mass, mineral-free lean mass (nonbone fat-free mass), fat mass, and truncal fat were measured using whole-body dual-energy x-ray absorptiometry.[29]

Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg et al.[30] Anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic artery and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of ≥ 1 additional contiguous segment), sectionectomy (resection of 2 Couinaud subsegments[31]), or segmentectomy (resection of 1 Couinaud subsegment). All of the nonanatomic procedures were classified as limited resection. One senior pathologist reviewed each specimen for histologic confirmation of the diagnosis. The width of the surgical margin was measured as the distance from the tumor edge to the line of resection. Perioperative and postoperative complications and deaths were recorded.

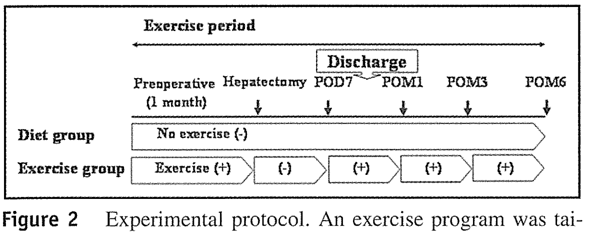

Figure 2 Experimental protocol. An exercise program was tailored for each patient. Exercise was started 1 month preoperatively, resumed from 1 week postoperatively, and continued for 6 months. Patients in both groups were given dietary advice. POD = postoperative day; POM = postoperative month.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD. Differences between 2 groups were assessed using χ^2 tests or Mann-Whitney *U* tests, as appropriate. The level of significance was set at $P < .05$. All statistical analyses were performed using SPSS for Windows version 11.0J (SPSS, Inc, Chicago, IL).

Results

The study included 51 patients (36 men, 15 women; mean age, 69.7 years). In a preliminary study, we examined the changes in PBF with exercise. PBF during exercise at the AT showed no significant changes from before (PBF rate, 24.3 $\pm$ 6.6 cm/s; PBF volume, 606 $\pm$ 168 mL/min) to immediately after exercise (PBF rate, 21.5 $\pm$ 4.1 cm/s; PBF volume, 579 $\pm$ 126 mL/min) or 1 hour after exercise (PBF rate, 23.6 $\pm$ 4.3 cm/s; PBF volume, 667 $\pm$ 80 mL/min) in healthy volunteers. However, PBF was significantly decreased on completion of exercise at one-third of the respiratory compensation point (PBF rates before, immediately after, and 1 hour after exercise, 24.0 $\pm$ 6.2, 14.9 $\pm$ 3.8, and 23.1 $\pm$ 3.4 cm/s, respectively; before vs immediately after, $P = .0472$, immediately after vs 1 hour after, $P = .0451$; PBF volumes before, immediately, and 1 hour after exercise, 588 $\pm$ 210, 386 $\pm$ 155, and 702 $\pm$ 230 mL/min, respectively; before vs immediately after, $P = .0105$, immediately after vs 1 hour after, $P = .0443$).

In patients with HCC with hepatic impairment exercising at the AT, portal flow showed no significant changes

(PBF rates before, immediately after, and 1 hour after exercise, 18.0 ± 4.7, 17.2 ± 3.6, and 18.3 ± 3.4 cm/s, respectively; PBF volumes before, immediately after, and 1 hour after exercise; 495 ± 290, 437 ± 139, and 504 ± 156 mL/min, respectively). Therefore, we concluded that exercise at the AT was safe for patients with HCC with hepatic impairment.

Preoperative characteristics

Table 1 summarizes the preoperative characteristics of the 2 groups of patients. There were no differences between the 2 groups with respect to age, gender, hepatitis virus status, Child-Pugh class, preoperative liver function (serum albumin, total bilirubin, cholinesterase, prothrombin time, platelet count, alanine aminotransferase, indocyanine green retention rate at 15 minutes, and ^{99m}Tc-diethylenetriamine penta-acetic acid-galactosyl human serum albumin Rmax), α-fetoprotein, protein induced by vitamin K absence/antagonism-II, and esophageal and/or gastric varices.

Perioperative parameters and pathologic findings

As shown in Table 2, the operating time, blood loss, blood transfusion, surgical procedures, postoperative complications, and hospital death rate did not differ significantly between the 2 groups. The postoperative hospital stay of the exercise group was shorter than that of the diet group, but not significantly. The pathologic findings of the 2 groups are also listed in Table 2. There were no differences between them with respect to tumor size, number of tumors, histology, microscopic capsule formation, microscopic vascular invasion, microscopic surgical margin <5 mm from the tumor border, associated liver diseases, and tumor-node-metastasis stage.

Physical and biochemical parameters

Whole body mass and body and fat mass at the waist were significantly decreased in the exercise group compared with the diet group after 6 months (Table 3). No differences were detected between the 2 groups with respect to the serum levels of protein (albumin and rapid turnover proteins) and lipids (triglycerides, total cholesterol, and low-density lipoprotein cholesterol) at 6 months postoperatively (data not shown). As an indicator of insulin resistance, fasting insulin, glucose, and HOMA-IR levels were measured before and after treatment (Fig. 3). In the exercise group, fasting serum insulin and HOMA-IR both showed significant decreases at 3 and 6 months postoperatively compared with the diet group. There were no differences between limited and anatomic resection on glucose, insulin, and HOMA-IR outcomes.

Comparison between standard and high-frequency exercise subgroups

Some patients failed to continue to exercise in the long term for various reasons (tumor recurrence, financial reasons, exacerbation of other diseases, etc). The changes in AT V_{O_2} and peak V_{O_2} after 6 months were significantly greater in the high-frequency exercise group than in the standard group (Table 4). The decreases in whole body mass and whole body fat mass were significantly greater in the high-frequency group. There were no significant

Table 1 Preoperative characteristics of the 2 groups of patients with HCC

Variable	Diet group (n = 26)	Exercise group (n = 25)	*P*
Age (y)	71.3 ± 8.8	68.0 ± 9.1	.1952
Men/women	19/7	17/8	.6908
HBV/HCV/NBC	4/18/4	6/11/8	.1823
Child-Pugh class (A/B)	25/1	24/1	.9774
Diabetes mellitus (yes/no)	3/23	3/22	.9592
ICGR15 (%)	16.8 ± 7.5	15.3 ± 8.0	.5098
Albumin (g/dL)	3.85 ± .32	3.93 ± .43	.4779
Total bilirubin (mg/dL)	.83 ± .23	.80 ± .20	.4172
Cholinesterase (U/L)	230 ± 65	237 ± 69	.4533
Prothrombin time (%)	90 ± 13	91 ± 10	.4080
Platelet count ($\times 10^4/\mu L$)	15.4 ± 8.9	16.0 ± 6.0	.6196
ALT (U/L)	46 ± 21	55 ± 33	.2325
GSA-Rmax (mg/min)	.460 ± .208	.469 ± .154	.2394
AFP (ng/mL)	694 ± 2,242	2,804 ± 10,176	.3166
PIVKA-II (mAU/mL)	711 ± 1,761	2,124 ± 5,620	.2461
Esophageal and/or gastric varices (yes/no)	7/19	8/17	.6908

Data are expressed as mean ± SD or as numbers of patients.
AFP = α-fetoprotein; ALT = alanine aminotransferase; GSA-Rmax = regional maximum removal rate of ^{99m}Tc-diethylenetriamine penta-acetic acid-galactosyl human serum albumin; HBV = hepatitis B virus; HCV = hepatitis C virus; ICGR15 = indocyanine green retention rate at 15 minutes; NBC = no hepatitis B or C virus; PIVKA-II = protein induced by vitamin K absence/antagonism-II.

Table 2 Operative and postoperative characteristics of the 2 groups of patients with HCC

Variable	Diet group (n = 26)	Exercise group (n = 25)	*P*
Surgical procedure (limited/anatomic)	16/10	14/11	.6879
Operating time (min)	326 ± 115	338 ± 152	.7404
Operative blood loss (mL)	986 ± 1,129	1,219 ± 1,767	.5811
Blood transfusion (yes/no)	3/23	4/21	.6435
Tumor size (cm)	4.10 ± 2.29	5.53 ± 5.33	.2230
Number of tumors	1.42 ± .70	1.40 ± .65	.9034
Histology (good/moderate/poor)	6/18/2	5/20/0	.3367
Microscopic capsule formation (yes/no)	21/5	22/3	.5466
Microscopic vascular invasion (yes/no)	14/12	12/13	.6763
Microscopic surgical margin (yes/no)	2/24	2/23	.9674
Associated liver disease (normal/fibrosis or hepatitis/cirrhosis)	3/14/9	5/11/9	.6568
Tumor stage (I or II/III or IV)	21/5	19/6	.6789
Morbidity (yes/no)	3/23	2/23	.6710
Mortality (yes/no)	0/26	0/25	
Postoperative hospital stay (d)	17.5 ± 11.3	13.7 ± 4.0	.1200

Data are expressed as mean ± SD or as numbers of patients.

changes in whole body fat-free mass ("muscle mass") in either group. Laboratory tests revealed that the platelet count at 6 months was significantly higher in the high-frequency group than in the standard group. Both fasting serum insulin and HOMA-IR showed significant decreases in the high-frequency group compared with the standard group. The branched-chain amino acid/tyrosine ratio was also significantly increased in the high-frequency group.

Comments

Rest has traditionally been considered essential for patients with chronic liver disease, because hard exercise causes a decrease in hepatic blood flow. However, attention has recently been paid to the negative effect of reduced muscle mass due to lack of exercise in patients with chronic liver disease.[32] In fact, when patients with liver disease performed exercise, there was no clinically important deterioration in hepatic function, and a slight improvement was actually observed.[33,34] It is known that physical activity reduces the risk for breast cancer and colon cancer and may also reduce the risk for several other types of cancer.[35–39] Regular exercise plays an important role in helping maintain a healthy body weight, while excess weight increases the circulating levels of estrogens, androgens, and insulin, all of which are associated with cell proliferation and tumor growth.[40] Physical activity may reduce the risk for cancer by decreasing circulating levels of insulin and insulin-like growth factors and by improving energy metabolism. Physical activity also helps prevent the occurrence of type 2 diabetes, which is associated with an increased risk for cancer of the colon, pancreatic cancer, and possibly other tumors.[41–44]

Table 3 Physiologic parameters of the 2 groups of patients with HCC

Variable	Whole body	Trunk	Waist	Hip
Body mass at 6 mo (% of baseline)				
Diet group	100 ± 4	99 ± 7	102 ± 8	99 ± 8
Exercise group	95 ± 5	95 ± 5	93 ± 7	96 ± 3
P	.0375*	.1119	.0028*	.0894
Fat mass at 6 mo (% of baseline)				
Diet group	97 ± 18	96 ± 18	99 ± 18	96 ± 17
Exercise group	86 ± 14	84 ± 15	82 ± 22	89 ± 14
P	.0685	.0595	.0365*	.2268
Fat-free mass at 6 mo (% of baseline)				
Diet group	100 ± 6	101 ± 7	105 ± 9	101 ± 9
Exercise group	101 ± 6	102 ± 9	102 ± 15	101 ± 7
P	.6492	.7422	.4822	.9479
Bone mineral density at 6 mo (% of baseline)				
Diet group	98 ± 3	95 ± 8	103 ± 12	92 ± 26
Exercise group	98 ± 3	97 ± 9	100 ± 17	98 ± 5
P	.9923	.6309	.6009	.4119

*Statistically significant ($P < .05$).

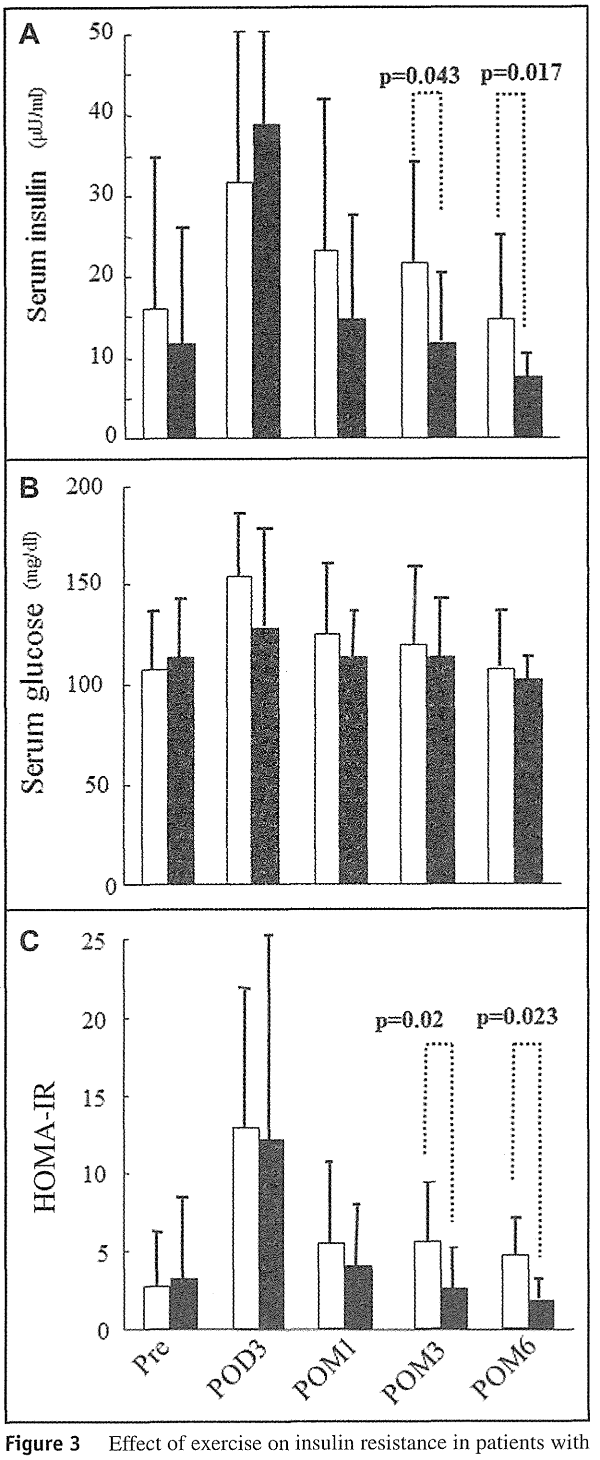

Figure 3 Effect of exercise on insulin resistance in patients with HCC with hepatic impairment. (A) Serum free insulin, (B) serum glucose, and (C) HOMA-IR in the diet group (white bars) and the exercise group (black bars). POD = postoperative day; POM = postoperative month.

However, there have been few reports about the effects of long-term exercise, and there have been no studies of perioperative exercise in patients with chronic hepatitis or cirrhosis undergoing hepatectomy for HCC. In the present study, exercise was started at approximately 1 month preoperatively, resumed approximately 1 week after surgery, and continued for 6 months at an intensity based on the AT of each patient. Each patient performed >3 60-minute exercise sessions weekly (mainly on a bicycle ergometer during hospitalization and by walking after discharge), and also received dietary guidance at 1, 3, and 6 months. Exercises mainly targeted the lower body, while upper-body muscle training was started from 2 months postoperatively to avoid wound pain. We hypothesized that exercise at the AT would reduce visceral fat and prevent loss of muscle mass. We found that the whole body mass and the fat mass at the waist both decreased significantly in the exercise group, while the skeletal muscle mass showed little change in either group (Table 3). No significant differences were detected between the 2 groups with respect to laboratory data such as lipids or rapid turnover proteins. None of the patients showed an increase of transaminases with exercise, and there were no clinical problems in the patients who performed exercise >3 times a week. At 3 and 6 months postoperatively, both serum insulin and the insulin resistance index showed significant improvement in the exercise group (Fig. 3).

It was recently reported that hepatic impairment, particularly cirrhosis, leads to secondary insulin resistance and hyperinsulinemia, which can then promote carcinogenesis. Management of insulin resistance is thus a critical issue for patients with chronic liver disease both to protect liver function and to prevent hepatocarcinogenesis. Alterations in glucose metabolism also affect fat metabolism, which may result in the excess production of lipid peroxide and reactive oxygen species,[45,46] which in turn damages hepatocytes,[17] leading to possible development of HCC.[46] However, it is difficult to manage insulin resistance associated with chronic liver disease because restriction of calorie intake conflicts with the need to overcome malnutrition arising from hepatocellular damage. A reduction in body weight with exercise has been reported to be advantageous in obese patients with chronic liver disease.[33] The present study had a short postoperative observation period, so no differences in the recurrence of HCC or of mortality were detected between the 2 groups (data not shown), but longer follow-up is necessary to confirm this finding.

When we divided the exercise group into standard and high-frequency subgroups on the basis of the weekly number of exercise sessions, AT V_{O_2} and peak V_{O_2} were significantly higher in the high-frequency group after 6 months. In addition, whole body mass and fat mass were significantly lower in the high-frequency group compared with the standard group at 6 months. Furthermore, the platelet count and branched-chain amino acid/tyrosine ratio were increased and the serum insulin/insulin resistance index ratio was significantly improved in the high-frequency group.

Table 4 Comparison of exercise tests, DEXA parameters, and laboratory data between the standard and high-frequency exercise subgroups

Variable	Standard (n = 11)	High frequency (n = 14)	*P*
Exercise parameters			
AT Vo_2 at 6 mo (% of baseline)	102 ± 14	115 ± 18	.0379*
Peak Vo_2 at 6 mo (% of baseline)	103 ± 12	118 ± 11	.0015*
DEXA parameters			
Whole body mass at 6 mo (% of baseline)	97 ± 4	93 ± 6	.0314*
Whole body fat mass at 6 mo (% of baseline)	98 ± 16	80 ± 15	.0075*
Whole body fat-free mass at 6 mo (% of baseline)	98 ± 6	103 ± 5	.0628
Laboratory data			
Albumin (g/dL)			
Pre	3.79 ± .52	3.98 ± .37	.3077
Post	4.09 ± .38	4.13 ± .31	.8055
Platelet count ($\times 10^4/\mu L$)			
Pre	18.8 ± 10.8	17.6 ± 4.9	.7362
Post	11.3 ± 2.5	14.8 ± 4.6	.0288*
ALT (U/L)			
Pre	56 ± 22	45 ± 37	.3898
Post	35 ± 33	31 ± 27	.7529
Insulin (μU/mL)			
Pre	9.1 ± 4.5	8.5 ± 5.8	.8099
Post	10.7 ± 4.6	5.8 ± 2.8	.0193*
Glucose (mg/dL)			
Pre	111 ± 16	117 ± 24	.5079
Post	101 ± 20	102 ± 10	.8991
HOMA-IR			
Pre	2.43 ± 1.12	2.59 ± 2.21	.8488
Post	2.71 ± 1.23	1.47 ± .68	.0232*
BCAA			
Pre	438 ± 102	462 ± 58	.4958
Post	474 ± 114	604 ± 214	.0960
AAA			
Pre	91 ± 19	80 ± 16	.1888
Post	102 ± 26	87 ± 13	.1184
BTR			
Pre	5.08 ± .84	5.43 ± .90	.4263
Post	4.78 ± 1.02	6.92 ± 2.20	.0091*

Data are expressed as mean ± SD.

AAA = aromatic amino acids; ALT = alanine aminotransferase; BCAA = branched-chain amino acids; BTR = branched-chain amino acid/tyrosine ratio; DEXA = dual-energy x-ray absorptiometric; HOMA-IR = homeostasis model of assessment of insulin resistance; Vo_2 = oxygen consumption.

*Statistically significant ($P < .05$).

One limitation of the present study was the selection of patients. The patients taking part in the study were less sick than many patients who might undergo this protocol, and patients with more advanced disease may not respond as well.

In conclusion, perioperative and postoperative exercise for patients with HCC with hepatic impairment led to weight loss (because of a decrease in fat mass) and improvement in insulin resistance but had no effect on skeletal muscle mass. Maintenance of postoperative physical strength and earlier resumption of daily activities could be possible by intensifying perioperative and postoperative exercise. We recommended that patients continue to exercise for 6 months after surgery. However, because some failed to continue to exercise long term for various reasons, patients should be followed up carefully after hepatectomy and encouraged to perform continuous long-term exercise.

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Clinicopathological Features of Recurrence in Patients After 10-year Disease-free Survival Following Curative Hepatic Resection of Hepatocellular Carcinoma

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Abstract

Background The present study aimed to clarify the clinicopathologic features of long-term disease-fee survival after resection of hepatocellular carcinoma (HCC).

Methods This retrospective study identified 940 patients who underwent curative resection of HCC between 1991 and 2000 at five university hospitals. Seventy-four patients with 10 years of recurrence-free survival were identified and followed up. They were divided into two groups, 60 recurrence-free and 14 with recurrence after a 10-year recurrence-free period.

Results Overall survival rates of recurrence and non-recurrence groups were 68 and 91 % at 16 years, and 34 and 91 % at 20 years ($p = 0.02$), respectively. There were five (36 %), and two deaths (3 %), respectively, after 10 recurrence-free years. A second resection for recurrence was performed in four patients (29 %), and mean survival was 15.3 years after the first hepatectomy. Although three patients in the non-recurrence group (5 %) developed esophageal and/or gastric varices, seven patients in the recurrence group (50 %) developed varices during 10 years ($p < 0.0001$). In multivariate analysis, preoperative and 10-year platelet count was identified as a favorable independent factor for maintained recurrence-free survival after a 10-year recurrence-free period following curative hepatic resection of HCC.

Conclusions Recurrence of HCC may occur even after a 10-year recurrence-free period. Long-term follow-up after resection of HCC is important, and should be life-long. Patients with higher preoperative and 10-year platelet counts are more likely to have long-term survival after resection. A low platelet count, related to the degree of liver fibrosis, is a risk factor for recurrence and survival of HCC after curative resection.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [1]. Although the incidence of HCC is highest in Asia and Africa, recent studies have shown that the incidence and mortality rates of HCC are also rising in North America and Europe [2, 3]. There has been an increase in the number of reports of nonsurgical therapeutic options for small HCC, such as percutaneous ethanol injection therapy [4], microwave coagulation therapy [5], and percutaneous radiofrequency ablation (RFA) [6], but there is ongoing controversy regarding the best method to treat small tumors. In Japan, liver transplantation is not a practical option for most HCC patients, because the national health insurance scheme only covers transplantation for patients with decompensated cirrhosis whose tumors fit the Milan criteria. Resection is therefore generally the first-line treatment for patients with small tumors and underlying chronic liver disease, but the long-term survival rate after potentially curative resection of HCC is still unsatisfactory because of the high rate of recurrence [7]. To improve prognosis, it is important to prevent the recurrence of HCC after its initial resection, but standard therapy for intrahepatic metastasis has not yet been developed. Therefore, the number of reports on long-term survivors after the initial hepatectomy remains small, especially on the basis of long-term (>10 years) observation of patients, with or without recurrence [8–12]. Furthermore, there are few reports regarding the characteristics of patients who survive without recurrence for at least 10 years after curative liver resection. In the present study, we retrospectively analyzed patients with long-term survival and compared them with patients who had recurrence of HCC after a 10-year disease-free period, in order to gain insight into the demography and biological behavior of HCC, and to identify the prognostic factors associated with survival.

Materials and methods

Subjects

Between 1991 and 2000, a total of 940 patients with HCC underwent curative resection (defined as macroscopic removal of all tumors) at five participating university hospitals. Thirty two patients died in the hospital and the remaining 908 were followed up as outpatients. Seventy-four patients (8 %) with 10-year recurrence-free survival after initial hepatectomy were included in this study. The median and mean duration of follow-up for the maximum time or until death was 12.6 and 13.3 years (range: 10.0–21.0 years). The median age of the patients at the initial hepatectomy was 59 years (range: 26–77 years). The 74 patients were stratified into a recurrence group and a recurrence-free group.

Clinicopathologic variables and surgery

Before surgery, each patient underwent conventional liver function tests, measurement of the indocyanine green retention rate at 15 min (ICGR15), and measurement of serum type IV collagen 7S. Hepatitis virus screening was done by measurement of hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb). The levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence/antagonism-II (PIVKA-II) were also measured in all patients. Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg et al. [13]. Accordingly, anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory, and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of two Couinaud subsegments [14]), or segmentectomy (resection of one Couinaud subsegment). All of the non-anatomically designated procedures were classified as limited resection, and were performed in patients with peripheral or central tumors and moderate liver dysfunction [15]. Patients with peripheral tumors and those with extrahepatic growths were treated by partial hepatectomy because this procedure achieved a sufficient surgical margin. In contrast, central tumors located near the hepatic hilum or major vessels were only treated by enucleation because it was too difficult and/or dangerous to remove enough liver tissue to obtain an adequate margin. A senior pathologist at each of the five participating university hospitals reviewed each specimen for histologic confirmation of the diagnosis. The width of the surgical margin was measured as the distance from the tumor edge to the resection line. The tumor stage was defined according to the TNM classification [16]. Histologic staging of fibrosis and grading of necroinflammation in the underlying liver was performed using the Knodell histologic activity index (HAI) [17] at the initial operation and at the second operation for those requiring repeat hepatectomy.

Follow-up

Perioperative/postoperative complications and deaths were recorded to determine the morbidity and mortality of hepatectomy. All surviving patients were followed up after discharge, with physical examination, liver function tests, ultrasonography, computed tomography (CT), or magnetic resonance imaging being performed at least every 3 months to check for intrahepatic recurrence, with chest radiographs obtained to detect pulmonary metastasis. A chest CT was performed if a chest radiograph showed any abnormalities. Bone metastases were diagnosed by bone scintigraphy.

When recurrence of HCC was detected from changes in tumor markers or from imaging findings, recurrence limited to the remnant liver was treated by transarterial chemoembolization (TACE), lipiodolization, second resection, or percutaneous local ablative therapy such as radiofrequency ablation (RFA). After detection of extrahepatic metastases, active treatment was performed in patients with a good hepatic functional reserve (Child-Pugh class A or B) and good performance status (0 or 1), while other patients were only given radiation therapy for bone metastases to relieve symptoms. Surgical resection was performed in patients with a solitary extrahepatic metastasis and no intrahepatic recurrence. In addition, all patients underwent endoscopy to evaluate the severity of esophageal and/or gastric varices before surgery and at 10 years after surgery.

Prognostic factors

We performed univariate and multivariate analysis of 28 clinicopathologic operative factors to identify independent variables related to the postoperative recurrence of HCC in patients with 10-year recurrence-free survival after curative hepatic resection. The factors investigated were gender, presence or absence of hepatitis C virus (HCV), and liver function (including albumin, alanine aminotransferase [ALT], and platelet count). The tumor factors studied were alpha fetoprotein (AFP), vitamin K absence or antagonist II (PIVKA-II), and histologic features (including tumor diameter, differentiation, vascular invasion, and associated liver disease). The operative factors that we assessed were operative blood loss, perioperative blood transfusion, and surgical procedure. All of the variables that were significant according to univariate analysis were then examined with a Cox proportional hazards model to identify variables that were independently associated with recurrence.

We also performed univariate and multivariate analysis of six clinical factors to identify independent variables related to postoperative recurrence of HCC more than 10 years after curative hepatic resection. The factors investigated were 10-year liver function (including albumin, aspartate aminotransferase [AST], ALT, and platelet count). The tumor factors studied were AFP and PIVKA-II.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. The significance of differences between the recurrence-free and recurrence groups was assessed by the Chi square test or the Mann–Whitney *U*-test, as appropriate. The Kaplan–Meier method was used to calculate the recurrence rate and overall survival rate as of December 2010, and the significance of differences in survival was estimated with the generalized log-rank test. The Cox regression model (stepwise method) was used for multivariate analysis. In all analyses, $p < 0.05$ was considered to indicate statistical significance.

Table 1 Preoperative and 10-year clinical characteristics of hepatocellular carcinoma (HCC) recurrence and non-recurrence groups

Variable	Non-recurrence group ($n = 60$)	Recurrence group ($n = 14$)	p value
Gender, male/female	47/13	13/1	0.21
Age, years	58.4 ± 9.8	58.9 ± 8.8	0.85
HBsAg (±)	16/44	3/11	0.69
HCVAb (±)	23/37	3/11	0.23
Child-Pugh class: A/B	57/3	13/1	0.75
Alcohol abuse (±)	19/41	5/9	0.77
Preoperative TACE (±)	36/24	9/5	0.77
ICGR15, %	11.9 ± 5.6	14.8 ± 5.9	0.16
Albumin, g/dL	4.1 ± 0.3	3.9 ± 0.3	0.08
Albumin (10 years), g/dL	4.1 ± 0.3	3.9 ± 0.4	0.10
Total bilirubin, mg/dL	0.79 ± 0.38	0.80 ± 0.24	0.91
Total bilirubin (10 years), mg/dL	0.75 ± 0.20	0.90 ± 0.60	0.81
Prothrombin time, %	100 ± 18	105 ± 28	0.54
Prothrombin time (10 years), %	102 ± 14	99 ± 19	0.90
Platelet count ($\times 10^4/\mu$L)	19.2 ± 7.3	13.3 ± 3.4	0.02
Platelet count (10 years) ($\times 10^4/\mu$L)	15.5 ± 4.1	12.1 ± 4.2	0.03
AST, IU/L	48 ± 44	38 ± 11	0.48
AST (10 years), IU/L	41 ± 26	55 ± 35	0.23
ALT, IU/L	57 ± 56	46 ± 26	0.56
ALT (10 years), IU/L	39 ± 27	63 ± 50	0.08
Type IV collagen 7S (10 years), ng/ml)[a]	4.93 ± 0.84	7.58 ± 0.79	0.002
AFP, ng/ml	311 ± 1198	918 ± 1646	0.12
AFP (10 years), ng/mL	9.3 ± 11.7	56.1 ± 104.1	0.04
PIVKA-II (mAU/mL)	601 ± 1626	38 ± 44	0.40
PIVKA-II (10 years), mAU/mL	25 ± 29	47 ± 61	0.21

Data presented as mean ± standard deviation (SD) or the number of patients. *HBsAg* hepatitis B surface antigen; *HCVAb* hepatitis C virus antibody; *TACE* transcatheter arterial chemoembolization; *ICGR15* indocyanine green retention rate at 15 min; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *AFP* α-fetoprotein; *PIVKA-II* protein induced by vitamin K absence/antagonism-II

[a] Indicated data were not available for all patients. The number of patients with the measurement was 34 and 6 in the non-recurrence and recurrence groups, respectively

Results

Preoperative and postoperative characteristics

Table 1 summarizes the preoperative characteristics of recurrence-free and recurrence groups. No difference was detected between the two groups with respect to gender, age, HBsAg, HCVAb, Child-Pugh class, alcohol abuse, preoperative TACE, ICGR15, and serum albumin, total bilirubin, prothrombin time, AST, ALT, AFP, or PIVKA-II. Postoperative characteristics at 10 years after surgery for each group are listed in Table 1. No difference was

Table 2 Changes in gastric and/or esophageal varices after 10 years of recurrence-free survival following curative hepatic resection

	Recurrence group (n = 14)				Non-recurrence group (n = 60)			
10 years after surgery: Before surgery	F0	F1	F2	F3	F0	F1	F2	F3
F0	7 (50 %)	5 (36 %)	0	0	54 (90 %)	3 (5 %)	0	0
F1	0	0	1 (7 %)	0	0	3 (5 %)	0	0
F2	0	0	0	1 (7 %)	0	0	0	0

detected between the two groups with respect to serum albumin, total bilirubin, prothrombin time, AST, ALT, and PIVKA-II. Patients in the non-recurrence group had a significantly higher platelet count preoperatively and at 10 years after surgery compared with those in the recurrence group. Patients in the non-recurrence group had significantly lower levels of type IV collagen 7S at 10 years after surgery compared with those in the recurrence group. Patients in the recurrence group had higher AFP levels at 10 years after surgery compared with those in the non-recurrence group. Table 2 shows the changes in esophageal and/or gastric varices after 10 years of recurrence-free survival following hepatic resection. Seven patients in the recurrence group (50 %) developed varices during the 10 years, while only three patients in the non-recurrence group (5 %) developed varices ($p < 0.0001$).

Surgical results and pathologic classification

The operating time, blood loss, blood transfusion requirement, procedures, and complications attributable to surgery did not differ significantly between the two groups. The pathologic features of each group are presented in Table 3. The number of tumors, tumor diameter, histology, associated liver disease, incidence of positive microscopic capsule formation, surgical margins, vascular invasion, and TNM stage did not differ significantly between the two groups.

Factors that influence recurrence of HCC after curative hepatic resection

Table 4 shows univariate and multivariate analyses of potential operative risk factors associated with recurrence of HCC in patients after a 10-year recurrence-free period following curative resection. Variables significantly associated with recurrence in the univariate and multivariate analyses were preoperative albumin ≤4.0 g/dL (odds ratio = 17.86; 95 % confidence interval (CI) = 1.64–42.0; p = 0.02), and preoperative platelet count ≤15 × 10^4/mL (odds ratio = 37.48; 95 % CI = 2.25–52.0; p = 0.01).

Table 5 shows univariate and multivariate analyses of potential 10-year risk factors associated with recurrence of HCC in patients after 10 years of recurrence-free survival following curative hepatic resection. Univariate and multivariate analyses showed that only platelet count ≤15 × 10^4/mL at 10 years after surgery (odds ratio = 12.92;

Table 3 Intraoperative and postoperative characteristics of the two groups

Variable	Non-recurrence group (n = 60)	Recurrence group (n = 14)	p value
Operating time, min	261 ± 77	284 ± 87	0.38
Operative blood loss, mL	1,095 ± 1129	1,508 ± 1,545	0.26
Blood transfusion (±)	18/42	4/10	0.92
Surgical procedure			
(Anatomic/limited resection)	32/28	5/9	0.24
Number of tumors (single/multiple)	55/5	13/1	0.88
Tumor size, cm	4.48 ± 3.98	3.16 ± 1.65	0.23
Histology (good/moderate/poor/necrosis)	11/30/15/4	3/5/3/3	0.70
Microscopic capsule formation (±)	50/10	13/1	0.37
Surgical margin (±)	8/52	0/14	0.60
Microscopic vascular invasion (±)	16/44	1/13	0.15
Associated liver disease			
(normal/fibrosis or hepatitis/cirrhosis)	21/31/8	3/8/3	0.55
TNM stage (I or II/III or IV)	48/12	12/2	0.62
Morbidity (±)	8/52	2/12	0.93

Data presented as mean ± SD or the number of patients

Table 4 Preoperative and operative risk factors predicting HCC recurrence in patients after 10 years of recurrence-free survival following curative hepatic resection

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
Male gender	3.60	0.43–20.1	0.24	–	–	–
HCV Ab	0.58	0.14–2.48	0.46	–	–	–
Albumin ≤4.0 g/dL	8.64	1.01–44.62	0.049	17.86	1.64–42.0	0.02
Platelet ≤15 × 10^4/mL	10.75	1.25–60.11	0.03	37.48	2.25–52.0	0.01
ALT >41 IU/L	2.50	0.55–11.11	0.24	–	–	–
AFP >10 ng/ml	1.33	0.41–4.31	0.63	–	–	–
PIVKA-II >40 mAU/mL	6.25	0.68–30.0	0.10	–	–	–
Operative blood loss >800 mL	3.85	0.15–14.67	0.26	–	–	–
Blood transfusion	3.90	0.85–17.82	0.08	9.56	0.68–33.61	0.09
Limited resection	2.51	0.74–8.48	0.14	–	–	–
Tumor size >3.4 cm	3.23	0.92–11.11	0.07	6.67	0.51–50.0	0.15
Vascular invasion	4.95	0.60–11.67	0.14	–	–	–
Poorly differentiated	0.90	0.22–3.71	0.88	–	–	–
Cirrhosis	0.67	0.13–3.39	0.63	–	–	–

CI confidence interval

Table 5 Risk factors at 10 years predicting HCC recurrence in patients after 10 years of recurrence-free survival following curative hepatic resection

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
Albumin ≤4.0 g/dL	4.50	0.89–22.75	0.07	7.69	0.70–43.33	0.10
Platelet ≤15 × 10^4/mL	6.06	1.11–33.33	0.04	12.92	1.08–63.91	0.04
AST >46 IU/L	1.46	0.34–6.35	0.62	–	–	–
ALT >47 IU/L	1.79	0.40–7.91	0.45	–	–	–
AFP >23 ng/mL	8.57	0.76–26.54	0.08	15.22	0.49–68.99	0.12
PIVKA-II >48 mAU/mL	7.29	0.64–32.64	0.11	–	–	–

95 % CI = 1.08–63.91; $p = 0.04$) was an independent predictor of recurrence of HCC.

In the non-recurrence group, the platelet count decreased at 1 year after curative hepatic resection, but there was no further marked decrease thereafter (Fig. 1). On the other hand, the platelet count in the recurrence group gradually decreased at 5 years after surgery. Patients in the non-recurrence group had a significantly higher platelet count preoperatively and at 7 and 10 years after surgery compared with those in the recurrence group.

Recurrence and survival

Figure 2 shows the recurrence status and therapeutic modalities used for disease recurrence in the 14 patients who had recurrence after a 10-year disease-free period.

Intrahepatic disease recurrence with fewer than three nodules and intrahepatic disease recurrence with more than three nodules were observed in 11 patients (79 %) and three patients (21 %), respectively. None of the patients were found to have an extrahepatic recurrence as the primary recurrence. The median and mean disease-free survival in the 14 patients with HCC recurrence was 11.0 and 11.6 years (range, 10.2–15.7 years), respectively, after the first hepatectomy (Fig. 3). The therapeutic modalities used included repeat hepatectomy in four patients (29 %), RFA in two patients (14 %), TACE in seven patients (50 %), and best supportive care in one patient (7 %). The HAI score in the underlying liver of these four patients changed from 1.0 ± 1.2 at first hepatectomy to 7.8 ± 1.3 at second resection ($p = 0.02$).

In the recurrence group, there were five deaths (36 %), four of which could be attributed to recurrence of HCC.

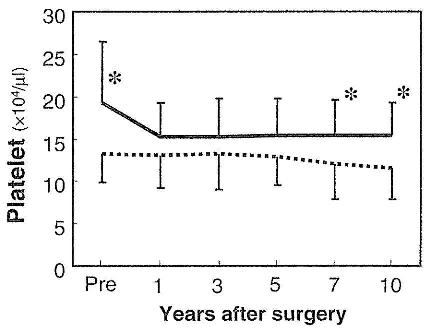

Fig. 1 Platelet count of recurrence and non-recurrence groups after hepatic resection. Data are shown as the mean ± SD. $^{*}p < .05$ versus the recurrence group at the corresponding time

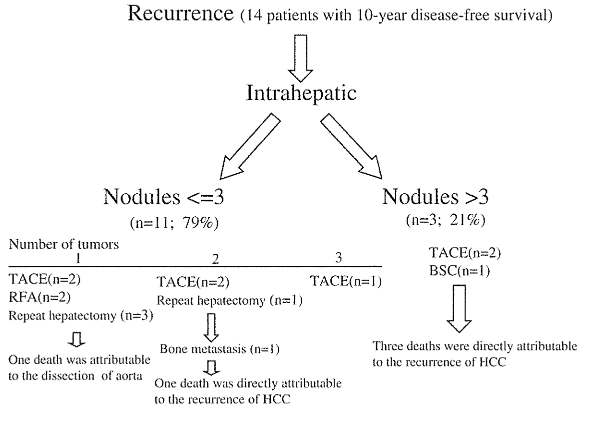

Fig. 2 Hepatocellular carcinoma (HCC) recurrence status and therapeutic modalities for treatment of recurrence in the 14 10-year disease-free survivors in whom late disease recurrence was detected. *RFA* percutaneous radiofrequency ablation; *BSC* best supportive care

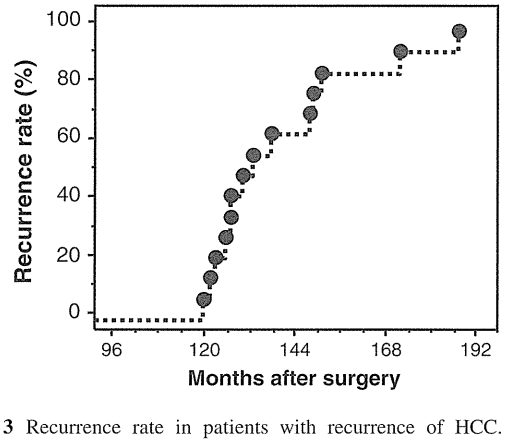

Fig. 3 Recurrence rate in patients with recurrence of HCC. The median and mean disease-free survival in the 14 patients with late disease recurrence was 11.0 and 11.6 years (range: 10.2–15.7 years) after the first hepatectomy

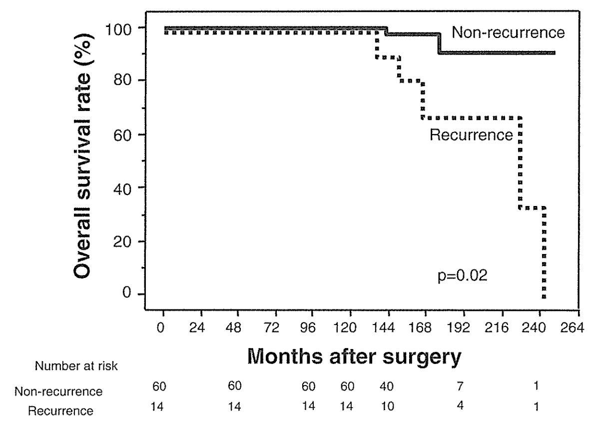

Fig. 4 Comparison of overall survival after hepatectomy in patients with or without recurrence of HCC. The survival rate of the recurrence group (*dotted line*) was significantly poorer than that of the non-recurrence group (*unbroken thin line*; $p = 0.02$). The number of patients at risk is shown below the graph

A second resection was performed in four patients, none of whom died, and median and mean survival was 15.0 and 15.3 years (range, 10.9–20.2 years), respectively, after the first hepatectomy. In the non-recurrence group, two of the 60 patients (3 %) died, with one death attributable to lung cancer at 11.9 years and the other to bile duct cancer at 14.7 years, respectively, after surgery. The overall survival rates of the recurrence and non-recurrence groups were 91 and 97 % at 12 years, 68 and 91 % at 16 years, and 34 and 91 % at 20 years, respectively (Fig. 4). There were significant differences ($p = 0.02$) in survival between the two groups.

Discussion

The recurrence rate of HCC after surgical resection is high, ranging from 50 to 100 % after 5 years in high-volume specialty centers worldwide [18–21]. Recently, close postoperative follow-up to detect recurrent HCC at an early stage, and various management strategies for recurrent HCC (including repeat resection, local ablative therapy, and/or TACE) have contributed to prolonged survival after initial hepatectomy [22–24]. Numerous studies to date have reported cumulative 5-year survival rates of approximately 40–50 %, based largely on relatively short-term follow-up [18, 22, 23, 25–27], and only a few reports of long-term follow-up of more than 10 years have been reported to date. Shimada et al. [11] reported 105 10-year survivors (21.8 %), including 42 disease-free survivors (8.7 %), among 578 patients. Fukuda et al. [12] reported that 29 of 250 patients survived for more than 10 years after initial hepatectomy, and 9 of those patients survived without