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Assessment of preoperative exercise capacity in hepatocellular carcinoma patients with chronic liver injury undergoing hepatectomy

Masaki Kaibori[1,5*], Morihiko Ishizaki[1], Kosuke Matsui[1], Richi Nakatake[1], Tatsuma Sakaguchi[1], Daiki Habu[2], Sawako Yoshiuchi[3], Yutaka Kimura[4] and A Hon Kon[1]

Abstract

Background: Cardiopulmonary exercise testing measures oxygen uptake at increasing levels of work and predicts cardiopulmonary performance under conditions of stress, such as after abdominal surgery. Dynamic assessment of preoperative exercise capacity may be a useful predictor of postoperative prognosis. This study examined the relationship between preoperative exercise capacity and event-free survival in hepatocellular carcinoma (HCC) patients with chronic liver injury who underwent hepatectomy.

Methods: Sixty-one HCC patients underwent preoperative cardiopulmonary exercise testing to determine their anaerobic threshold (AT). The AT was defined as the break point between carbon dioxide production and oxygen consumption per unit of time (VO_2). Postoperative events including recurrence of HCC, death, liver failure, and complications of cirrhosis were recorded. Univariate and multivariate analyses were performed to evaluate associations between 35 clinical factors and outcomes, and identify independent prognostic indicators of event-free survival and maintenance of Child-Pugh class.

Results: Multivariate analyses identified preoperative branched-chain amino acid/tyrosine ratio (BTR) <5, alanine aminotransferase level ≥42 IU/l, and AT VO_2 <11.5 ml/min/kg as independent prognostic indicators of event-free survival. AT VO_2 <11.5 ml/min/kg and BTR <5 were identified as independent prognostic indicators of maintenance of Child-Pugh class.

Conclusions: This study identified preoperative exercise capacity as an independent prognostic indicator of event-free survival and maintenance of Child-Pugh class in HCC patients with chronic liver injury undergoing hepatectomy.

Keywords: Liver cancer, Chronic liver injury, Hepatectomy, Exercise capacity, BCAA/tyrosine ratio

Background

Major surgery has been shown to increase oxygen demand by about 40%, which may place severe stress on cardiopulmonary reserve [1]. Patients with high cardiopulmonary risk have traditionally been assessed using tests such as transthoracic echocardiography, dobutamine stress echocardiography, radionuclide ventriculography, and spirometry. However, these assessments have not been validated as preoperative screening tests, and provided mostly static measurements of cardiopulmonary performance [2-4]. Walking distance or ability to climb stairs have been used as subjective measurements of exercise tolerance, and have been shown to predict perioperative complications [5,6]. However, these measurements lack objectivity and do not detect silent cardiopulmonary abnormalities. Dynamic assessment of preoperative exercise capacity may be a useful predictor of short- and long-term postoperative prognosis. Cardiopulmonary exercise (CPX) testing measures oxygen uptake at increasing levels of work and predicts cardiopulmonary performance under conditions of stress, such as after surgery. In elderly patients undergoing major abdominal surgical procedures, the majority of deaths from cardiopulmonary complications

* Correspondence: kaibori@hirakata.kmu.ac.jp
[1]Department of Surgery, Hirakata Hospital, Kansai Medical University, 573-191 Hirakata, Osaka, Japan
[5]Masaki Kaibori, Department of Surgery, Hirakata Hospital, Kansai Medical University, 2-3-1 Shinmachi, 573-1191 Hirakata, Osaka, Japan
Full list of author information is available at the end of the article

occur in patients with an anaerobic threshold (AT) of <11 ml/min/kg [7,8].

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [9]. Maintenance of good perioperative nutrition and metabolism may improve the prognosis of patients with HCC undergoing hepatectomy [10,11]. To date, few studies have examined the usefulness of preoperative CPX testing in patients undergoing hepatectomy. In the present study, we aimed to clarify whether preoperative exercise capacity was related to event-free survival in HCC patients with chronic liver injury undergoing hepatectomy.

Methods

Patients

HCC patients with chronic hepatitis or cirrhosis who were scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between December 2008 and April 2010 were screened for inclusion this study. A total of 66 HCC patients underwent curative resection (defined as macroscopic removal of all tumor). There was no in-patient mortality. Sixty-one of the 66 patients were analyzed in this study, and the other 5 were excluded because they were followed up at other hospitals. All patients gave written informed consent for participation in this study. The study protocol was approved by the institutional ethics committee.

Cardiopulmonary exercise testing

Patients underwent preoperative CPX testing using a bicycle ergometer with an incremental protocol (5.0, 7.5, and 10 W/min). Twelve-lead electrocardiography was used to monitor heart rate, ST segment deviation, and arrhythmias, at rest and continuously during the exercise and recovery periods. Blood pressure was recorded at rest and every 2 min during the exercise and recovery periods. Peak oxygen consumption per unit of 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, indicating the onset of metabolic acidosis, was defined as the break point between carbon dioxide production and VO_2 [12], 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 [13]. Thus, AT was set at the time of maximum fat combustion [14]. 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 [15]. Exercise was stopped when the patient requested it because of fatigue, pain, or headache, or if there was failure to maintain a speed greater than 40 rpm for more than 30 seconds despite encouragement.

Clinical variables and surgery

Before surgery, each patient underwent conventional liver function testing and measurement of the indocyanine green retention rate at 15 min (ICGR15). Hepatitis virus infection screening was performed by testing for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb). Alpha-fetoprotein (AFP) and protein induced by vitamin K absence/antagonism-II (PIVKA-II) levels were measured in all patients. We used two methods to determine body composition: dual-energy X-ray absorptiometry (DEXA) [16] and bioelectrical impedance analysis (BIA) [17]. Total body mass, mineral-free lean mass (non-bone fat-free mass), fat mass, and truncal fat were measured by whole body DEXA. BIA was performed using the whole body 8-electrode approach with a 5-500 kHz multifrequency impedance analyzer (InBody720, BIOSPACE Co., Ltd, Tokyo, Japan). Intracellular body water (ICW), extracellular water (ECW), total body water (TBW), body cell mass, and ECW ratio (ECW/TBW) were measured.

Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg et al. [18]. Anatomic resection was defined as resection of the tumor together with the related portal vein branches and corresponding hepatic territory, and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (right trisectionectomy, or similar procedures on the left or for smaller resections), sectionectomy (resection of two Couinaud sub-segments [19]), or segmentectomy (resection of one Couinaud subsegment). All other procedures were classified as nonanatomical resection, which was frequently performed for peripheral or central tumors. Peripheral tumors and those with extrahepatic growth were treated by partial hepatectomy because this procedure achieved a sufficient surgical margin. Central tumors located near the hepatic hilum or major vessels were treated by enucleation only, because it was too difficult and/or dangerous to remove enough liver tissue to obtain adequate margins. One consultant pathologist reviewed all specimens 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.

Follow-up

Peri- and postoperative complications and deaths were recorded to determine morbidity and mortality following hepatectomy. Postoperative complications were defined and classified according to the modified Clavien system [20]. Briefly, Grade I was any deviation from the normal postoperative course that did not require special treatment, Grade II required pharmacological treatment, Grade III required surgical or radiological intervention without (IIIa) or with (IIIb) general anesthesia, Grade IV was any life-threatening complication involving dysfunction of one (IVa) or multiple (IVb) major organs, and Grade V was death. Postoperative liver-related events recorded included recurrence of HCC, HCC-related death, postoperative liver failure, and complications of cirrhosis requiring hospitalization (hepatic encephalopathy, uncontrollable pleural effusion or ascites, and rupture of esophageal or gastric varices). The Child-Pugh class of every patient was determined preoperatively and every 6 months postoperatively.

All surviving patients were followed up at least every 3 months after discharge. Follow-up included physical examination, liver function testing, chest radiographs to check for pulmonary metastases, and ultrasonography, computed tomography, or magnetic resonance imaging to check for intrahepatic recurrence. Chest computed tomography was performed if the chest radiograph showed any abnormalities. Bone metastases were diagnosed by bone scintigraphy.

When recurrence of HCC was detected by changes in tumor markers or on imaging, recurrence limited to the remnant liver was treated by transarterial chemoembolization, lipiodolization, re-resection, or percutaneous local ablative therapy such as radiofrequency ablation. When extrahepatic metastases were detected, active treatment was undertaken in patients with 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 to relieve symptoms of bone metastases. Surgical resection was undertaken in patients with a solitary extrahepatic metastasis and no intrahepatic recurrence.

Prognostic factors

We performed univariate and multivariate analyses of 35 clinical factors to identify independent variables related to postoperative event-free survival and postoperative maintenance of Child-Pugh class. The patient factors investigated were gender, age, body mass index, alcohol abuse, HBsAg, HCVAb, non-hepatitis B or C virus infection, diabetes mellitus, white blood count, lymphocyte count, insulin, homeostasis model assessment of insulin resistance, and liver function (including albumin, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], prothrombin time, cholinesterase, platelet count, alkaline phosphatase, ICGR15, total cholesterol, low density lipoprotein cholesterol, transferrin, transthyretin, retinol-binding protein [RBP], transthyretin [TTR], branched chain amino acid [BCAA]/tyrosine ratio [BTR], and Child-Pugh class). The tumor factors investigated were AFP and PIVKA-II. The exercise parameters investigated were AT, VO_2, and peak VO_2. The body composition parameters investigated using DEXA were body mass, fat mass, fat-free mass, and whole-body mineral density. The body composition parameters investigated using BIA were ICW, ECW, TBW, protein, mineral, body fat mass, and body cell mass.

All the variables that were identified as significantly associated with event-free survival or maintenance of Child-Pugh class by univariate analyses were then examined using the Cox proportional hazards model to identify variables that were independently associated with event-free survival or maintenance of Child-Pugh class.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). The significance of differences between groups was assessed using the chi-square test or Mann–Whitney *U*-test, as appropriate. The Kaplan-Meier method was used to calculate rates of event-free survival and maintenance of Child-Pugh class as of February 2012, and the significance of differences in survival rates was estimated using the generalized log-rank test. The Cox proportional hazards regression model (stepwise method) was used for multivariate analyses. In all analyses, $p < 0.05$ was considered statistically significant.

Results

This study included 61 patients (45 male, 16 female; mean ± SD age = 70 ± 9 years). Table 1 shows the perioperative characteristics of HCC patients. Postoperative complications were observed in five patients: Grade II complications in three patients (ascites and/or pleural effusion) and Grade IIIa complications in two patients (intra-abdominal abscess). We followed these 61 patients until February 2012, with a median follow-up time of 24 months (range 12-36 months). We analyzed the prognostic factors associated with event-free survival and maintenance of Child-Pugh class. Postoperative events were defined as death due to recurrence of HCC, recurrence of HCC, intractable pleural effusion or ascites, gastrointestinal bleeding, or hepatic encephalopathy. Of the 61 patients, seven died from recurrence of HCC, 22 developed recurrence of HCC, two developed intractable pleural effusion or ascites, two developed gastrointestinal bleeding, and two developed hepatic encephalopathy.

Child-Pugh class changed from class A preoperatively to class B postoperatively in nine patients, from class A to class C in one patient, and from class B to class C in one patient.

Table 1 Perioperative characteristics of HCC patients

Age (years)	70 ± 9
Gender (male/female)	45/16
HBV/HCV/NBC	12/32/15
Child-Pugh class (A/B)	56/5
Diabetes mellitus (+/−)	8/53
WBC count (/μl)	5,000 ± 1,319
Lymphocyte count (/μl)	1,484 ± 580
ICGR15 (%)	16.1 ± 7.8
Albumin (g/dl)	3.8 ± 0.4
Total bilirubin (mg/dl)	0.81 ± 0.21
Cholinesterase (U/l)	232 ± 64
Triglyceride (mg/dl)	85 ± 43
Prothrombin time (%)	92 ± 12
Platelet count (×10^4/μl)	15 ± 8
AST (U/l)	43 ± 27
ALT (U/l)	42 ± 28
RBP (mg/dl)	3.3 ±1.4
TTR (mg/dl)	16 ±6
BTR	5.09 ± 1.46
AFP (ng/ml)	994 ± 5,028
PIVKA-II (mAU/ml)	1,283 ± 2,209
Esophageal and/or gastric varices (+/−)	15/46
Surgical procedure (limited/anatomic)	35/26
Operation time (min)	329 ± 130
Operative blood loss (ml)	1,011 ± 1,351
Blood transfusion (+/−)	9/52
Tumor size (cm)	4.42 ± 4.09
Associated liver disease	
(normal/fibrosis or hepatitis/cirrhosis)	9/30/22
Morbidity (+/−)	5/56

Data represent the mean ± standard deviation or the number of patients. *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NBC* non-hepatitis B or C virus, *WBC* white blood cell, *ICGR15* indocyanine green retention rate at 15 min; *ALT* alanine aminotransferase, *RBP* retinol binding protein, *TTR* transthyretin, *BTR* branched chain amino acid/tyrosine ratio, *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence/antagonism-II.

Factors associated with event-free survival and maintenance of child-pugh class

The preoperative factors significantly associated with event-free survival on univariate analyses were preoperative ALT, albumin, RBP, BTR, platelet count, AT VO_2, peak VO_2, ICW, body cell mass, and total body protein (Table 2). The preoperative factors associated with maintenance of Child-Pugh class on univariate analyses were albumin, BTR, triglyceride, and AT VO_2. Multivariate analyses (Cox proportional hazards model) of the factors associated with event-free survival on univariate analyses identified preoperative BTR <5, ALT ≥42 IU/l, and AT VO_2 <11.5 ml/min/kg as independent prognostic indicators of event-free survival (Table 3). Multivariate analyses (Cox proportional

Table 2 Results of univariate analyses of potential prognostic factors for event-free survival in HCC patients

Variable	No. of patients	1-year survival rate (%)	3-year survival rate (%)	p value
Etiology				
HBV	13	91.7	52.1	0.1144
HCV	33	78.1	29.0	
NBC	15	86.7	54.2	
AST (IU/l)				
≤43	30	83.3	45.6	0.1961
>43	31	82.8	28.3	
ALT (IU/l)				
≤42	30	93.1	53.3	0.01
>42	31	73.3	22.2	
Albumin (g/dl)				
≥3.8	34	87.9	51.0	0.0226
<3.8	27	76.9	11.5	
RBP (mg/dl)				
≥3.3	32	86.7	46.9	0.0210
<3.3	29	77.8	77.8	
BTR				
≥5.0	33	87.5	53.0	0.0238
<5.0	28	77.8	16.2	
Platelet count (10^4/μl)				
≥15	32	85.7	52.1	0.0355
<15	29	80.6	20.9	
AT VO_2 (ml/min/kg)				
≥11.5	32	90.3	42.3	0.0266
<11.5	29	75.0	33.4	
Peak VO_2 (ml/min/kg)				
≥16.5	32	87.1	50.3	0.0331
<16.5	29	78.6	10.8	
Intracellular body water (l/BW kg)				
≥0.33	32	90.3	35.8	0.0129
<0.33	29	75.0	30.3	
Body cell mass (kg/BW kg)				
≥0.47	32	90.3	34,0	0.0359
<0.47	29	75.0	33.3	
Total body protein (kg/BW kg)				
≥0.14	35	85.3	36.3	0.1071
<0.14	26	78.3	32.2	

HBV hepatitis B virus, *HCV* hepatitis C virus, *NBC* non-hepatitis B or C virus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *RBP* retinol binding protein, *BTR* branched chain amino acid/tyrosine ratio, *AT* anaerobic threshold, *VO_2* oxygen consumption, *BW* body weight.

Table 3 Results of multivariate analyses of potential prognostic factors for event-free survival in patients with HCC

Variable	Coefficient	SE	Relative risk	*p* value
BTR (≥5 vs. < 5)	1.240	0.415	3.454	0.0028
ALT (≥42 vs. < 42 IU/l)	1.045	0.418	2.841	0.0124
AT VO_2 (≥11.5 vs. < 11.5 ml/min/kg)	1.004	0.412	2.730	0.0148

SE standard error, *BTR* branched chain amino acid/tyrosine ratio, *ALT* alanine aminotransferase, *AT* anaerobic threshold, VO_2 oxygen consumption.

hazards model) of factors associated with maintenance of Child-Pugh class on univariate analyses identified preoperative AT VO_2 <11.5 ml/min/kg and BTR <5 as independent prognostic indicators of maintenance of Child-Pugh class.

Figure 1 shows that there was a significant correlation between BTR and AT VO_2 in HCC patients (r = 0.410, Y = 8.139 + 0.583 * X, $p = 0.0019$).

Outcomes

There was a significant difference in the event-free survival rate between patients with preoperative BTR ≥5.0 and <5.0 ($p = 0.0238$) (Figure 2A). There was also a significant difference in the rate of maintenance of Child-Pugh class between patients with preoperative BTR ≥5.0 and <5.0 ($p = 0.0494$) (Figure 2B).

There was a significant difference in the event-free survival rate between patients with AT VO_2 ≥11.5 and <11.5 ml/min/kg ($p = 0.0266$) (Figure 3A). There was also a significant difference in the rate of maintenance of Child-Pugh class between patients with AT VO_2 ≥11.5 and <11.5 ml/min/kg ($p = 0.0464$) (Figure 3B).

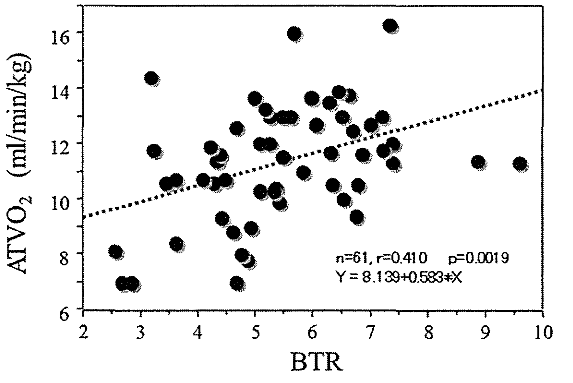

Figure 1 Relationships between preoperative BTR and AT VO_2 in HCC patients. There was a significant correlation between BTR and AT VO_2 (r = 0.410, Y = 8.139 + 0.583 * X, $p = 0.0019$). *BTR* branched chain amino acid/tyrosine ratio, *AT VO_2* anaerobic threshold oxygen consumption.

Discussion and conclusions

We examined the relationships among preoperative CPX parameters, postoperative events including recurrence of HCC, and change in Child-Pugh class in 61 patients undergoing hepatectomy. The variables derived from CPX testing included peak VO_2, which is the maximum oxygen uptake at peak exercise. Previous studies indicated that peak VO_2 was the most useful predictor of postoperative cardiopulmonary complications in patients undergoing radical esophagectomy with three-field lymphadenectomy [21] and patients undergoing surgical procedures for lung cancer [22-26]. The AT is defined as the point during exercise at which oxygen demand outstrips oxygen delivery and metabolism starts to become anaerobic. AT is a measure of the ability of the cardiopulmonary system to deliver adequate oxygen to tissues, and has the advantage of being independent of patient motivation. Reaching AT does not require high levels of physical stress and occurs well before peak VO_2 [27]. The usefulness of measuring AT has been assessed predominantly in elderly patients undergoing major surgical procedures, allowing the development of an operative risk grading and treatment protocol [7,8]. An AT cut-off of 11 ml/min/kg, which is internationally recognized, is currently used to select patients for enhanced recovery programs after colorectal surgery. However, AT has not been found to be useful in the assessment of cardiopulmonary fitness of patients undergoing esophagectomy only [21].

This study identified AT VO_2 <11.5 ml/min/kg as an independent prognostic indicator of both event-free survival and maintenance of Child-Pugh class, indicating that CPX testing can be used to prospectively evaluate the cardiopulmonary function of HCC patients with chronic liver injury undergoing hepatectomy. It is possible that CPX testing can be used to predict postoperative recurrence of HCC or liver dysfunction. It has recently been reported that hepatic impairment, particularly cirrhosis, leads to secondary insulin resistance and hyperinsulinemia, resulting in the promotion of carcinogenesis. Management of insulin resistance is therefore critical in patients with chronic liver disease, to protect liver function and prevent hepatocarcinogenesis. Alterations in glucose metabolism also affect fat metabolism (production of lipid peroxide and reactive oxygen species) [28,29], which in turn may damage hepatocytes [30], leading to possible development of HCC [31]. It is difficult to manage insulin resistance associated with chronic liver disease, because restriction of caloric intake conflicts with the need to overcome malnutrition arising from hepatocellular damage. However, a reduction in body weight with exercise has been reported to be advantageous in obese patients with chronic liver disease [32]. The results of these studies and of our

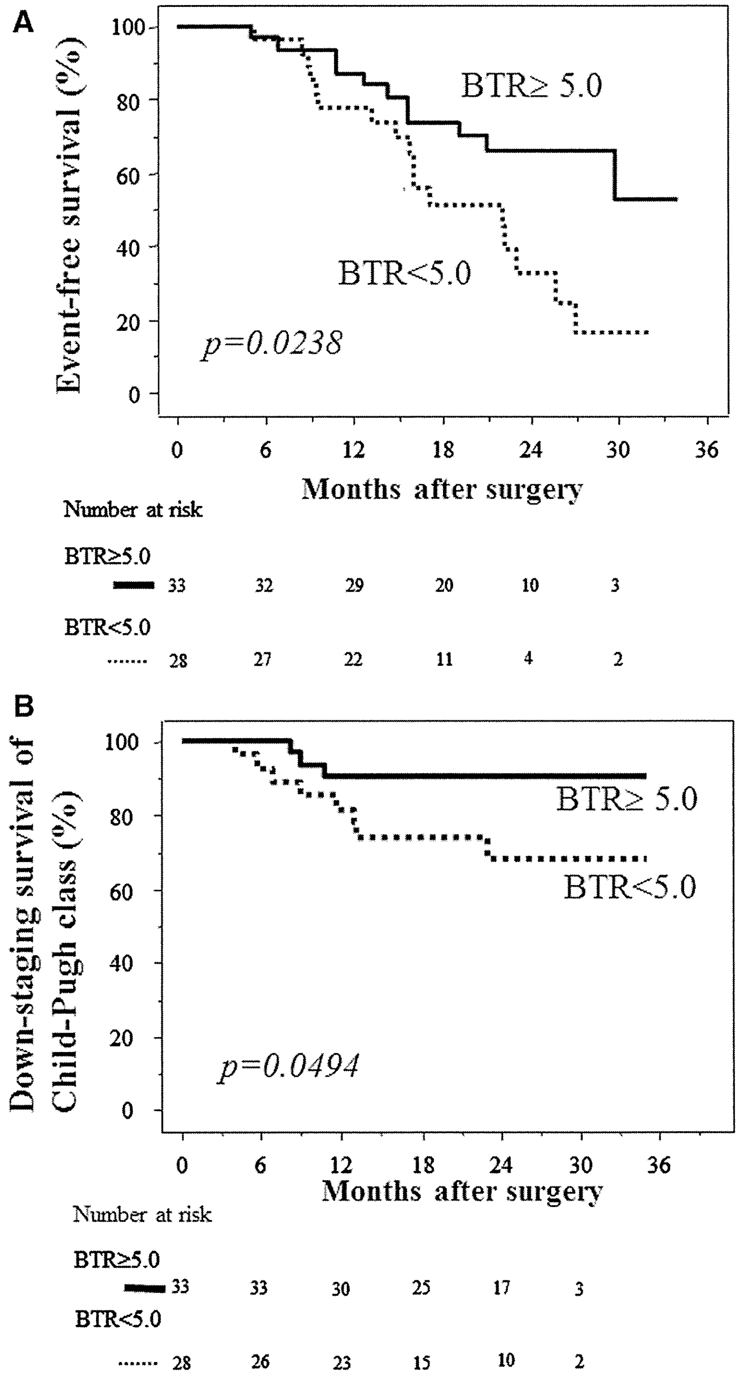

Figure 2 Comparisons of event-free survival and maintenance of Child-Pugh class after hepatectomy between patients with preoperative BTR ≥5.0 and <5.0. (A) Event-free survival. The survival rate was significantly higher in patients with preoperative BTR ≥5.0 (solid line) than BTR <5.0 (dotted line) ($p = 0.0238$). **(B)** Maintenance of Child-Pugh class. The rate of maintenance of Child-Pugh class was significantly higher in patients with preoperative BTR ≥5.0 (solid line) than BTR <5.0 (dotted line) ($p = 0.0494$). The numbers of patients at risk are shown below each graph. *BTR* branched chain amino acid/tyrosine ratio.

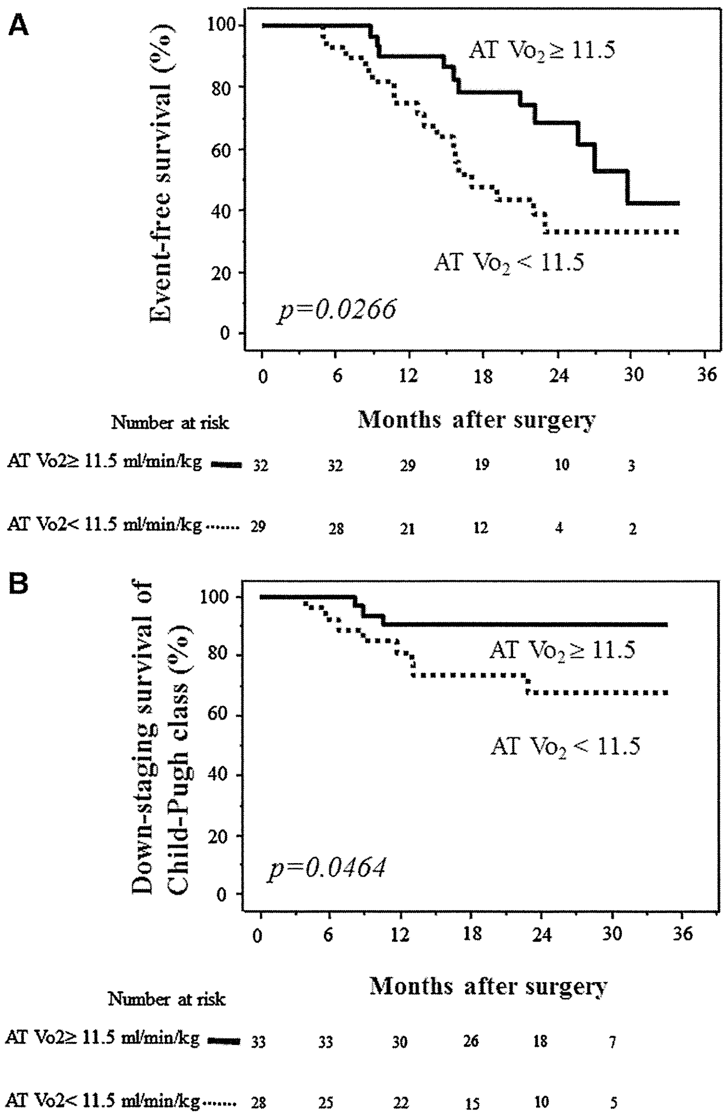

Figure 3 Comparisons of event-free survival and maintenance of Child-Pugh class after hepatectomy between patients with preoperative AT VO_2 ≥11.5 ml/min/kg and <11.5 ml/min/kg. (A) Event-free survival. The survival rate was significantly higher in patients with preoperative AT VO_2 ≥11.5 ml/min/kg (solid line) than AT VO_2 <11.5 ml/min/kg (dotted line) ($p = 0.0266$). **(B)** Maintenance of Child-Pugh class. The rate of maintenance of Child-Pugh class was significantly higher in patients with preoperative AT VO_2 ≥11.5 ml/min/kg (solid line) than AT VO_2 <11.5 ml/min/kg (dotted line) ($p = 0.0464$). The numbers of patients at risk are shown below each graph. *AT VO_2* anaerobic threshold oxygen consumption.

study indicate that hepatectomy for HCC patients with cirrhosis can be safely performed in patients with AT VO_2 ≥11.5 ml/min/kg.

When liver function is impaired, metabolism of amino acids is also impaired. Consumption of BCAAs in skeletal muscle is increased to compensate for the lack of energy production by the liver [33], and aromatic amino acids (AAAs) are abundant. The balance of BCAAs and AAAs is known as the Fischer ratio [34]. The tyrosine level alone can be used instead of the AAA level to determine BTR [33]. BTR decreases in patients with liver dysfunction, such as chronic hepatitis or cirrhosis [35-37]. BTR can therefore be used as a marker of liver function in patients with liver disease [33,35-37]. BTR also has a high degree of correlation with other markers of liver function [36,37]. In the present study, we found that BTR was an independent prognostic indicator of recurrence of HCC or progressive liver dysfunction. Prolonged BCAA supplementation can therefore improve the prognosis of HCC patients who have undergone hepatectomy. It is important to pay attention to the preoperative BTR when planning perioperative care. We found a significant correlation between BTR and AT VO_2 in HCC patients.

In conclusion, preoperative exercise capacity and BTR were identified as independent prognostic indicators of event-free survival and maintenance of Child-Pugh class in HCC patients with chronic liver injury undergoing hepatectomy. These results suggest that pre- and postoperative intervention with exercise therapy and BCAA supplementation may be beneficial in patients with chronic liver injury.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MK conducted the data analysis and drafted the manuscript. DH, YK and AHK conceived of the study, participated in its design, and helped draft the manuscript. MI, RN and TS participated in the study design and contributed to the data collection. KM participated in the study design and advised the analysis. SY contributed to study data collection. All authors contributed to the interpretation of the findings, and read and approved the final manuscript.

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Synopsis for table of contents
In patients with hepatocellular carcinoma and hepatic dysfunction who underwent liver resection, preoperative exercise capacity and branched-chain amino acid/tyrosine ratio were identified as independent prognostic indicators of event-free survival and maintenance of Child-Pugh class. Improvement of preoperative exercise capacity may influence the short- and long-term postoperative prognosis in patients with chronic liver injury. Pre- and postoperative exercise therapy and branched-chain amino acid supplementation may be beneficial in these patients.
The study protocol was approved by the institutional ethics committee of Kansai Medical University (reference number: KMU H101036 and 080916).

Author details
[1]Department of Surgery, Hirakata Hospital, Kansai Medical University, 573-191 Hirakata, Osaka, Japan. [2]Department of Nutritional Medicine, Graduate School of Human Life Science, Osaka City University, 545-8585 Osaka, Japan. [3]Department of Nutrition Management, Hirakata Hospital, Kansai Medical University, 573-191 Hirakata, Osaka, Japan. [4]Health Science Center, Hirakata Hospital, Kansai Medical University, 573-191 Hirakata, Osaka, Japan. [5]Masaki Kaibori, Department of Surgery, Hirakata Hospital, Kansai Medical University, 2-3-1 Shinmachi, 573-1191 Hirakata, Osaka, Japan.

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ORIGINAL ARTICLE

Novel Liver Visualization and Surgical Simulation System

Masaki Kaibori · Yen-Wei CHEN · Kosuke Matsui · Morihiko Ishizaki · Takumi Tsuda · Richi Nakatake · Tatsuma Sakaguchi · Hideyuki Matsushima · Kosuke Miyawaki · Tsukasa Shindo · Tomoko Tateyama · A-Hon Kwon

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Abstract
Background Successful liver surgery requires an understanding of the patient's particular liver characteristics, including shape and vessel distribution. In clinical medicine, there is a high demand for surgical assistance systems to assess individual patients. Our aims in this study were to segment the liver based on computed tomography volume data and to develop surgical plans for individual patients.
Methods 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.
Results The 3D visualization of the liver allowed easy recognition of vessel and tumor location and selection of these structures with the 3D pointing device. The surgeon's prior knowledge and clinical experience were integrated into the visualization system to create a practical virtual surgery, leading to improved functionality and accuracy of information recognition in the surgical simulation system.
Conclusions The 3D visualization demonstrated details of individual liver structure, resulting in better understanding and practical surgical simulation.

Keywords 3D visualization · Liver · Hepatectomy · Surgical simulation

Introduction

The complex distribution of vessels in the human liver and the significant individual variations in liver size and shape can complicate liver surgery. To ensure safe and appropriate surgery, it is essential to understand the liver structure and vessel distribution unique to the individual during preoperative surgical planning. With the recent development of medical imaging equipment, imaging data can be obtained with a resolution of 0.5 mm, providing detailed information about internal organ structure and any possible abnormalities. Imaging data play an important role in the examination of abnormal regions, in the early diagnosis of disease, and in surgical planning.

Using high-resolution medical images, we studied 3D visualizations of human organs and surgery planning systems.[1–4] The MeVis Company in Germany has developed a visualization system that semi-automatically extracts the liver and hepatic vessels from computed tomography (CT) volume data.[5] However, a more practical surgery simulation system that can adapt to different surgical scenarios is necessary for efficient presurgical planning and for use in the training of doctors and medical students. Our aims were to simulate practical liver surgical procedures using a 3D display and to construct a surgical planning assistance system for surgeons, interns, and medical students. The system we

M. Kaibori (✉) · K. Matsui · M. Ishizaki · T. Tsuda · R. Nakatake · T. Sakaguchi · H. Matsushima · A.-H. Kwon
Department of Surgery, Hirakata Hospital, Kansai Medical University, 2-3-1 Shinmachi, Hirakata, Osaka 573-1191, Japan
e-mail: kaibori@hirakata.kmu.ac.jp

Y.-W. CHEN · K. Miyawaki · T. Shindo · T. Tateyama
Intelligent Image Processing Lab, College of Information Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan

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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.

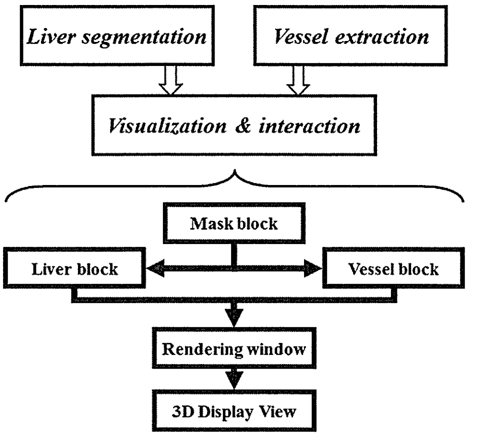


Fig. 1 Flow chart of our liver surgery visualization and simulation system

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.

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.

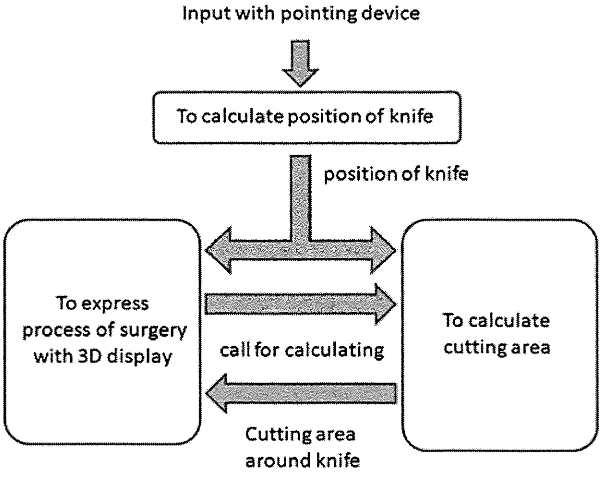


Fig. 2 Flow chart of surgical simulation

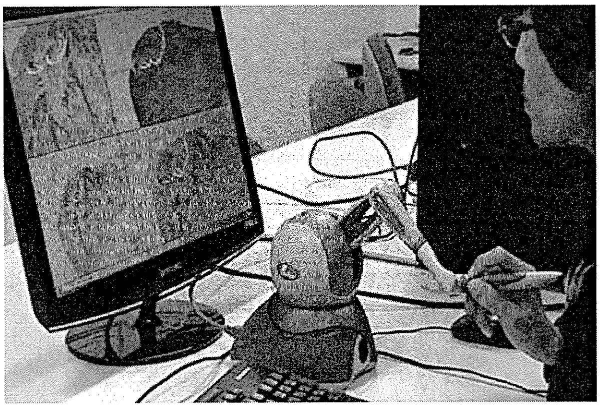


Fig. 3 The surgical simulation system and its screens

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

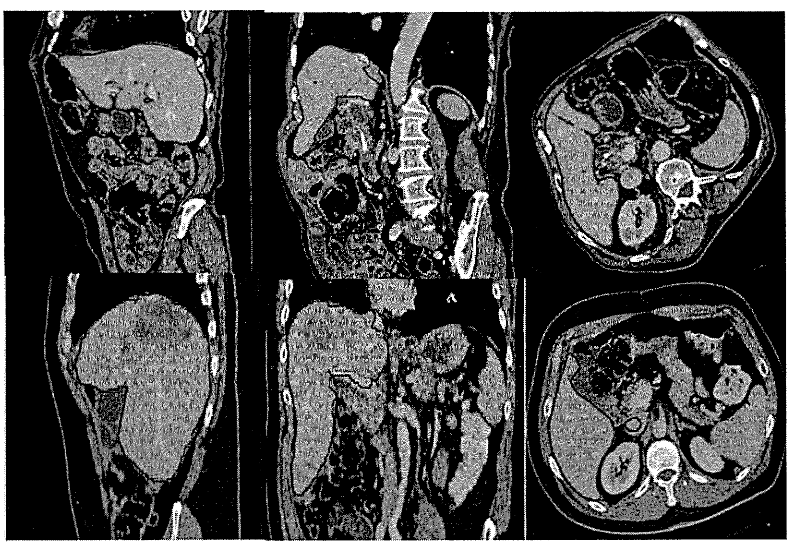
Almost all medical visualization systems to date have used the Visualizing Tool Kit (VTK) library.[6] However, VTK is only used for CPU processing and its processing time is long, making it unsuitable for an interactive surgical simulation system. To accelerate the speed of visualization and interaction, 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



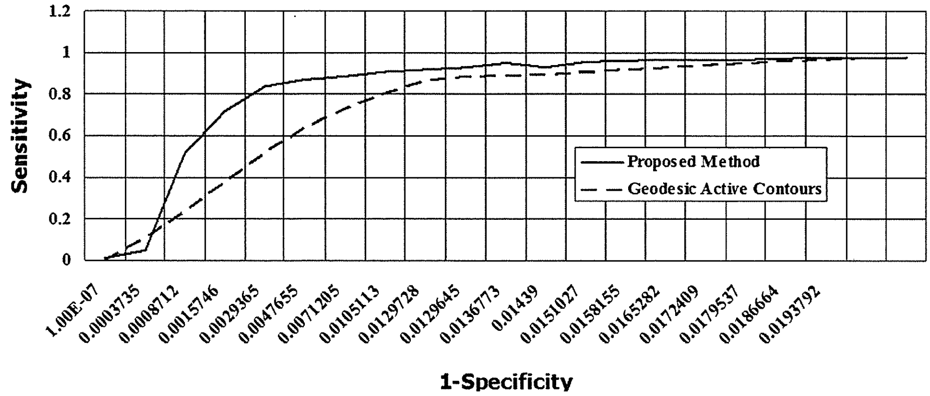


Fig. 5 Comparison of ROC curves. ROC curves comparing the results of the liver segmentation by our method and the geodesic active contour method

(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

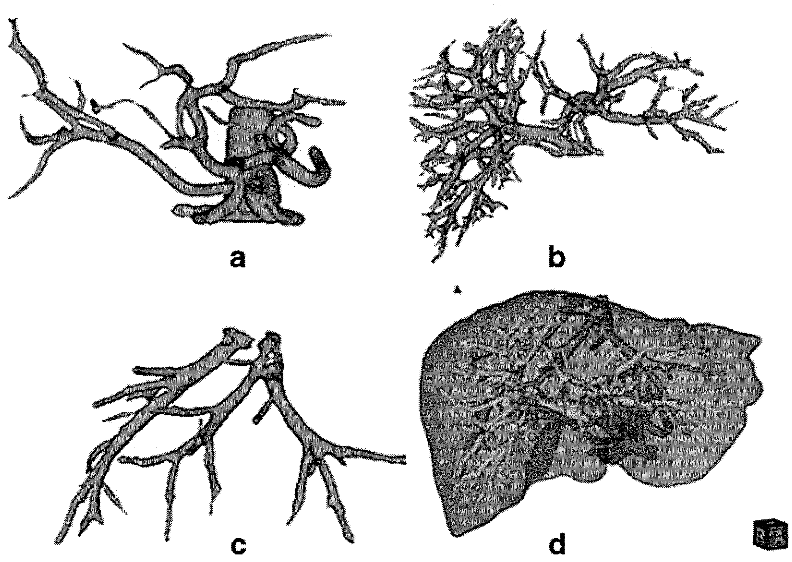


Fig. 6 Iso-surface visualization of the liver and its vascular structure. **a** Hepatic artery. **b** portal vein. **c** hepatic vein. **d** liver and its vascular structure. In **d**, the hepatic artery, portal vein, and hepatic vein are colored in *red*, *yellow*, and *blue*, respectively

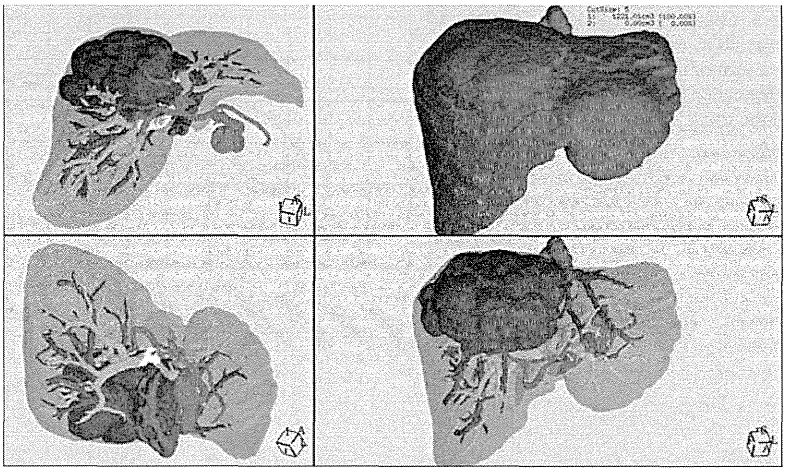


Fig. 7 Surgical simulation results. A case of right trisectionectomy for hepatocellular carcinoma. Artery (*red*), portal vein (*yellow*), hepatic vein (*blue*), and hepatocellular carcinoma (*dark brown*)

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

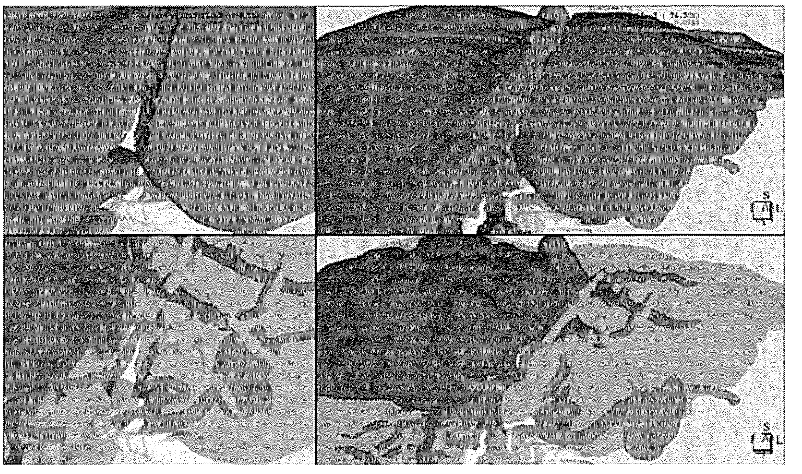


Fig. 9 Surgical simulation of liver parenchymal dissection

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

Masaki Kaibori, M.D.[a,*], Morihiko Ishizaki, M.D.[a], Kosuke Matsui, M.D.[a], Richi Nakatake, M.D.[a], Sawako Yoshiuchi, R.D.[b], Yutaka Kimura, M.D.[c], A-Hon Kwon, M.D.[a]

[a]Department of Surgery, [b]Department of Nutrition Management, [c]Health Science Center, Hirakata Hospital, Kansai Medical University, 2-3-1 Shinmachi, Hirakata, Osaka 573-1191, Japan

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

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* Corresponding author. Tel.: +81-72-804-0101 ext. 56130; fax: +81-72-804-0170.

E-mail address: kaibori@hirakata.kmu.ac.jp

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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.

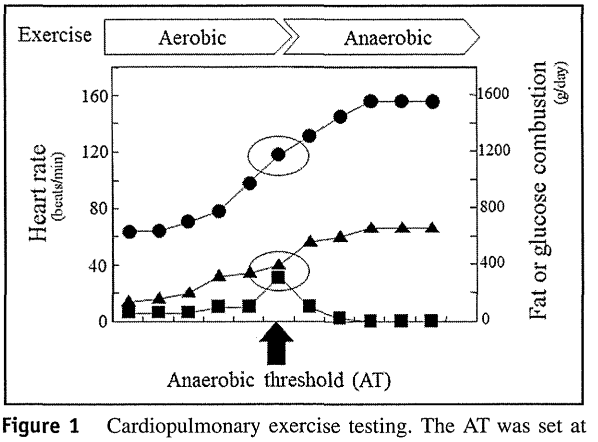

Figure 1 Cardiopulmonary exercise testing. The AT was set at the break point between carbon dioxide production and Vo_2, or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective nadirs before beginning to increase again. Thus, the 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) × 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.

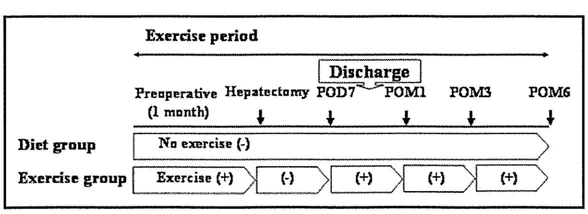

Figure 2 Experimental protocol. An exercise program was tailored for each patient. Exercise was started 1 month preoperatively, resumed from 1 week postoperatively, and continued for 6 months. Patients in both groups were given dietary advice. POD = postoperative day; POM = postoperative month.

Statistical analysis

Continuous variables are presented as mean ± 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 ± 6.6 cm/s; PBF volume, 606 ± 168 mL/min) to immediately after exercise (PBF rate, 21.5 ± 4.1 cm/s; PBF volume, 579 ± 126 mL/min) or 1 hour after exercise (PBF rate, 23.6 ± 4.3 cm/s; PBF volume, 667 ± 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 ± 6.2, 14.9 ± 3.8, and 23.1 ± 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 ± 210, 386 ± 155, and 702 ± 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.