HCC.[27,28] Further, AFP and DCP are directly associated with HCC progression through the induction of cancer cell proliferation and angiogenesis, respectively.[29,30] Thus, our results are in good accordance with previous basic investigations and suggest that hepatic inflammation as well as elevated AFP and DCP levels independently accelerate the progression of NBNC-HCC.

Diagnostic year of HCC was also directly associated with the Milan criteria in this study. Although the reason for this association is unclear, a progress in serum tumor markers is a possible explanation. Because sensitivities of AFP and DCP were improved during this study period (1995–2006),[31–33] one would think that serum AFP and DCP levels are confounding factors for an association between diagnostic year of HCC and the Milan criteria.

Recently, lifestyle-related factors including alcohol intake and diabetes mellitus have been noted as risk factors for the development of NBNC-HCC.[2,10–12,34–38] Previous *in vitro* studies showed that ethanol and glucose stimulate the proliferation and migration of HCC,[39,40] indicating the direct association of alcohol intake and diabetes mellitus with NBNC-HCC progression. However, in this study, these factors were not directly associated with the Milan criteria. Although the reason for this discrepancy remains unclear, alcohol intake and diabetes mellitus were associated with the Milan criteria through diagnosis of liver cirrhosis in this study. Both ethanol consumption and diabetes mellitus can activate fibroblasts,[41,42] which are crucial components of the tumor microenvironment promoting the growth and invasion of cancer cells.[43,44] Thus, alcohol intake and diabetes mellitus may be associated with the clinical progression of NBNC-HCC through the tumor microenvironment.

Then, we created a decision tree algorithm to identify the clinical feature profiling associated with the staging of NBNC-HCC; the reproducibility of this model was confirmed by the independent validation datasets. Serum AFP level was selected for the initial classification, and serum DCP level was selected for the third division, creating groups 3 and 4. Although it is still unclear why the serum AFP level was associated with the Milan criteria to a greater extent than the serum DCP level, an association of the serum AFP level with the pathological features of HCC is a possible explanation. The AFP level is related to the number of HCC, whereas the DCP level is more specific to vascular invasion.[45–47] In this study, the staging of HCC was evaluated by using the Milan criteria, which include number and size of HCC but not vascular invasion,[26] explaining why serum AFP level was selected for the initial classification.

Diagnosis of liver cirrhosis was selected for the second division in the decision tree algorithm. Although liver cirrhosis is a well-known major risk factor for the development of HCC,[5,10,12,25,34,42] our result indicates that liver cirrhosis may suppress the progression of NBNC-HCC. We do not have any data accounting for the association between diagnosis of liver cirrhosis and suppression of the NBNC-HCC progression, the following is, however, a possible explanation for this contradiction. HCC surveillance may be performed more often in patients with liver cirrhosis than in those without liver cirrhosis,[12,25] so HCC could be identified at an early stage in patients with liver cirrhosis.

A limitation of this study is that a relationship between progression of NBNC-HCC and non-alcoholic steatohepatitis (NASH) was not evaluated. The reason is that NASH-related HCC is often diagnosed as cryptogenic cirrhosis-related HCC because of reduction of hepatic triglycerides according to the progression of NASH, so-called "burned-out NASH".[48] However, NASH is deeply involved in the development of HCC and a major reason for the increase in number of NBNC-HCC patients.[8,49,50] Recently, visceral fat accumulation is also reported to be an independent risk factor for HCC recurrence after curative treatment.[51] Thus, further study will be focused on a relationship between the progression of NBNC-HCC and NASH.

In conclusion, data mining disclosed complex associations of risk factors and clinical feature profiling associated with the staging of NBNC-HCC.

REFERENCES

1 El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008; **134**: 1752–63.
2 Kawaguchi T, Taniguchi E, Itou M, Sumie S, Yamagishi SI, Sata M. The pathogenesis, complications and therapeutic strategy for hepatitis C virus-associated insulin resistance in the era of anti-viral treatment. *Rev Recent Clin Trials* 2010; **5**: 147–57.
3 Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010; **51**: 1820–32.
4 Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. *Intervirology* 2010; **53**: 39–43.
5 Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis* 2010; **42** (Suppl 3): S206–14.
6 Nouso K, Kobayashi Y, Nakamura S *et al.* Evolution of prognostic factors in hepatocellular carcinoma in Japan. *Aliment Pharmacol Ther* 2010; **31**: 407–14.

7 Tanaka H, Imai Y, Hiramatsu N *et al.* Declining incidence of hepatocellular carcinoma in Osaka, Japan, from 1990 to 2003. *Ann Intern Med* 2008; **148**: 820–6.
8 Taura N, Fukushima N, Yatsuhashi H *et al.* The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased in Kyushu area. *Med Sci Monit* 2010; **17**: PH7–11.
9 Abe H, Yoshizawa K, Kitahara T, Aizawa R, Matsuoka M, Aizawa Y. Etiology of non-B non-C hepatocellular carcinoma in the eastern district of Tokyo. *J Gastroenterol* 2008; **43**: 967–74.
10 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35–50.
11 Hassan MM, Hwang LY, Hatten CJ *et al.* Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206–13.
12 Kiyosawa K, Umemura T, Ichijo T *et al.* Hepatocellular carcinoma: recent trends in Japan. *Gastroenterology* 2004; **127**: S17–26.
13 Bellazzi R, Zupan B. Predictive data mining in clinical medicine: current issues and guidelines. *Int J Med Inform* 2008; **77**: 81–97.
14 Kalisch M, Fellinghauer BA, Grill E *et al.* Understanding human functioning using graphical models. *BMC Med Res Methodol* 2010; **10**: 14–23.
15 Edwards D. *Introduction to Graphical Modelling*. New York: Springer-Verlag, 2000.
16 Pielou EC. *The Interpretation of Ecological Data. A Primer on Classification and Ordination*, 1st edn. New York: John Wiley&Sons, Inc., 1984.
17 Legendre P, Legendre L. *Numerical Ecology*, 2nd edn. Amsterdam: Elsevier Science, 1998.
18 Tsai CL, Camargo CA Jr. Methodological considerations, such as directed acyclic graphs, for studying "acute on chronic" disease epidemiology: chronic obstructive pulmonary disease example. *J Clin Epidemiol* 2009; **62**: 982–90.
19 Kurosaki M, Matsunaga K, Hirayama I *et al.* A predictive model of response to peginterferon ribavirin in chronic hepatitis C using classification and regression tree analysis. *Hepatol Res* 2010; **40**: 251–60.
20 Kurosaki M, Sakamoto N, Iwasaki M *et al.* Pretreatment prediction of response to peginterferon plus ribavirin therapy in genotype 1 chronic hepatitis C using data mining analysis. *J Gastroenterol* 2010 (in press).
21 Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med* 1980; **302**: 1109–17.
22 Lee A, Joynt GM, Ho AM, Keitz S, McGinn T, Wyer PC. Tips for teachers of evidence-based medicine: making sense of decision analysis using a decision tree. *J Gen Intern Med* 2009; **24**: 642–8.
23 Guo J, Wang W, Liao P *et al.* Identification of serum biomarkers for pancreatic adenocarcinoma by proteomic analysis. *Cancer Sci* 2009; **100**: 2292–301.
24 Warwick J, Vardaki E, Fattizzi N *et al.* Defining the surgical management of suspected early-stage ovarian cancer by estimating patient numbers through alternative management strategies. *BJOG* 2009; **116**: 1225–41.
25 Kudo M, Okanoue T. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. *Oncology* 2007; **72** (Suppl 1): 2–15.
26 Mazzaferro V, Regalia E, Doci R *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693–9.
27 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57–70.
28 Sanz-Cameno P, Trapero-Marugan M, Chaparro M, Jones EA, Moreno-Otero R. Angiogenesis: from chronic liver inflammation to hepatocellular carcinoma. *J Oncol* 2010; article no.: 272170.
29 Inagaki Y, Tang W, Xu H *et al.* Des-gamma-carboxyprothrombin: clinical effectiveness and biochemical importance. *Biosci Trends* 2008; **2**: 53–60.
30 Wang XW, Xie H. Alpha-fetoprotein enhances the proliferation of human hepatoma cells in vitro. *Life Sci* 1999; **64**: 17–23.
31 Weitz IC, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. *Hepatology* 1993; **18**: 990–7.
32 Fujiyama S, Tanaka M, Maeda S, Ashihara H, Hirata R, Tomita K. Tumor markers in early diagnosis, follow-up and management of patients with hepatocellular carcinoma. *Oncology* 2002; **62** (Suppl 1): 57–63.
33 Marrero JA, Lok AS. Newer markers for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S113–19.
34 El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 2007; **37** (Suppl 2): S88–94.
35 El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; **126**: 460–8.
36 Kawaguchi T, Sata M. Importance of hepatitis C virus-associated insulin resistance: therapeutic strategies for insulin sensitization. *World J Gastroenterol* 2010; **16**: 1943–52.
37 Kawaguchi T, Taniguchi E, Morita Y *et al.* Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. *Liver Int* 2010; **30**: 479–86.
38 Tazawa J, Maeda M, Nakagawa M *et al.* Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. *Dig Dis Sci* 2002; **47**: 710–15.
39 Brandon-Warner E, Sugg JA, Schrum LW, McKillop IH. Silibinin inhibits ethanol metabolism and ethanol-dependent cell proliferation in an in vitro model of hepatocellular carcinoma. *Cancer Lett* 2010; **291**: 120–9.
40 Chang YJ, Chiu CC, Wu CH *et al.* Glucose-regulated protein 78 (GRP78) silencing enhances cell migration but does not influence cell proliferation in hepatocellular carcinoma. *Ann Surg Oncol* 2010; **17**: 1703–9.

41 Flanders KC. Smad3 as a mediator of the fibrotic response. *Int J Exp Pathol* 2004; **85**: 47–64.
42 Gyamfi MA, Wan YJ. Pathogenesis of alcoholic liver disease: the role of nuclear receptors. *Exp Biol Med (Maywood)* 2010; **235**: 547–60.
43 Pietras K, Ostman A. Hallmarks of cancer: interactions with the tumor stroma. *Exp Cell Res* 2010; **316**: 1324–31.
44 Xing F, Saidou J, Watabe K. Cancer associated fibroblasts (CAFs) in tumor microenvironment. *Front Biosci* 2010; **15**: 166–79.
45 Hamamura K, Shiratori Y, Shiina S *et al.* Unique clinical characteristics of patients with hepatocellular carcinoma who present with high plasma des-gamma-carboxy prothrombin and low serum alpha-fetoprotein. *Cancer* 2000; **88**: 1557–64.
46 Miyaaki H, Nakashima O, Kurogi M, Eguchi K, Kojiro M. Lens culinaris agglutinin-reactive alpha-fetoprotein and protein induced by vitamin K absence II are potential indicators of a poor prognosis: a histopathological study of surgically resected hepatocellular carcinoma. *J Gastroenterol* 2007; **42**: 962–8.
47 Toyoda H, Kumada T, Kiriyama S *et al.* Prognostic significance of simultaneous measurement of three tumor markers in patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2006; **4**: 111–17.
48 Ong J, Younossi ZM, Reddy V *et al.* Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl* 2001; **7**: 797–801.
49 Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972–8.
50 Hashimoto E, Yatsuji S, Kaneda H *et al.* The characteristics and natural history of Japanese patients with nonalcoholic fatty liver disease. *Hepatol Res* 2005; **33**: 72–6.
51 Ohki T, Tateishi R, Shiina S *et al.* Visceral fat accumulation is an independent risk factor for hepatocellular carcinoma recurrence after curative treatment in patients with suspected NASH. *Gut* 2009; **58**: 839–44.

A prospective randomized controlled trial of hemostasis with a bipolar sealer during hepatic transection for liver resection

Masaki Kaibori, MD, Kosuke Matsui, MD, Morihiko Ishizaki, MD, Tatsuma Sakaguchi, MD, Hideyuki Matsushima, MD, Yoichi Matsui, MD, *and* **A-Hon Kwon, MD,** *Osaka, Japan*

Background. *Excessive intraoperative blood loss and the possible requirement for blood transfusion are major problems in hepatic resection for liver tumors. The decrease of blood loss is a goal in liver surgery, and several technical developments have been introduced for this purpose. The aim of this prospective randomized study was to compare the use of the Cavitron Ultrasonic Surgical Aspirator (CUSA) with a radiofrequency-based bipolar hemostatic sealer versus CUSA with standard bipolar cautery (BC) in patients undergoing hepatic resection.*

Methods. *One hundred nine patients with liver tumors were randomized to undergo hepatic transection via CUSA with a bipolar sealer (Aquamantys 2.3 Bipolar Sealer;* n = *55) or BC* (n = *54). Blood loss during parenchymal transection and speed of transection were the primary end points, whereas the degree of postoperative liver injury and morbidity were secondary end points.*

Results. *Compared with the BC group, the bipolar sealer showed lesser blood loss during transection and blood loss divided by resection area* (P = *.0079 and .0008, respectively), shorter transection time* (P = *.0025), faster speed of transection* (P < *.0001), and fewer ties and ties divided by resection area required during transection* (P < *.0001).*

Conclusion. *CUSA with a bipolar sealer is superior to CUSA with standard BC for various hepatectomy in terms of less blood loss and faster speed of transection, with no increase in morbidity. (Surgery 2013;154:1046-52.)*

Department of Surgery, Hirakata Hospital, Kansai Medical University, Hirakata, Osaka, Japan

SEVERAL DIFFERENT OPERATIVE DEVICES for hepatic transection and coagulation have been proposed with the aim to minimize intraoperative blood loss, which is associated with an increased rate of postoperative morbidity and mortality, as well as with decreased long-term survival.[1,2] Most blood loss occurs during parenchymal transection.[3] Several techniques have been developed for safe and careful parenchymal dissection. The popular devices facilitating bloodless transection include standard bipolar cautery (BC; B. Braun Aesculap Japan, Bunkyo-ku, Tokyo),[4] the Cavitron Ultrasonic Surgical Aspirator (CUSA; Tyco Healthcare, Mansfield, MA), which uses ultrasonic energy,[5] and the radiofrequency (RF) coagulator (TissueLink; TissueLink Medical, Inc, Dover, NH), which uses RF energy.[6] In Several previous studies, researchers investigated the role of these different operative devices in hepatic transection compared with the traditional clamp-crushing technique or CUSA.[7-9]

Indeed, hepatic transection by the clamp-crushing technique or CUSA is safe and simple and can be performed with different coagulators. The bipolar sealer used in the current study is a relatively new device that delivers RF energy coupled with saline solution irrigation for hemostatic sealing at lower temperatures (<100°C) than conventional electrocautery devices. This device functions to shrink the collagen in the walls of the tissue vessels without causing charring or burning, in contrast to standard electrocautery.[10] Several clinical applications of this bipolar sealer have

This RCT study was registered with the UMIN Clinical Trials Registry (UMIN-CTR) on April 1, 2011 (Registration number UMIN000005325).

Accepted for publication April 25, 2013.

Reprint requests: Masaki Kaibori, MD, Department of Surgery, Hirakata Hospital, Kansai Medical University, 2-3-1 Shinmachi, Hirakata, Osaka 573-1191, Japan. E-mail: kaibori@hirakata.kmu.ac.jp.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2013.04.053

been reported in the literature, including its use in orthopedic oncology procedures,[11] total hip,[10] and total knee arthroplasty,[12,13] spinal procedures,[14] and pulmonary resection.[15]

The bipolar seems less efficient in sealing the vascular structures encountered during dissection, and it may produce necrosis on the cut surface, which may be a source of morbidity. In contrast, BC seems to be one of the most widely used procedures and a more economic coagulation device in liver procedures. The aim of this prospective randomized study was to compare the use of CUSA with a bipolar sealer versus CUSA with BC in patients undergoing hepatic resection.

METHODS

Patients. All patients scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between August 2010 and January 2012 were screened for this study. The inclusion criteria were elective hepatectomy, age of >18 and <80 years, adequate cardiopulmonary and renal function, and ability to provide written informed consent. Patients with portal vein tumor thrombus or previous portal vein embolization and those in whom portal vein resection was anticipated were excluded. Patients with ruptured hepatocellular carcinoma (HCC), those undergoing repeat hepatectomy, and those in whom concomitant bowel or bile duct resection was anticipated also were excluded.

Before the operation, each patient underwent conventional liver function tests and measurement of the indocyanine green retention rate at 15 minutes. Hepatitis screening was performed by measurement of hepatitis B surface antigen and hepatitis C antibody. The levels of α-fetoprotein and protein induced by vitamin K absence or antagonist-II were also measured. Preoperative radiologic assessment always included computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis.

Operative techniques. Operations were classified according to the Brisbane terminology proposed by Strasberg et al.[16] Anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory. Anatomic resection procedures were classified as hemihepatectomy (right hemihepatectomy was defined as resection of Couinaud subsegments[17] V–VIII, and left hemihepatectomy was defined as resection of subsegments II–IV), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of 2 Couinaud subsegments), or segmentectomy (resection of one Couinaud subsegment).

All nonanatomic procedures performed for both peripheral and central tumors were classified as limited resection. Peripheral tumors and tumors with extrahepatic growth were treated by partial hepatectomy because in using this method we were able to achieve a resection margin wider than 1 cm. Conversely, central tumors located near the hepatic hilum or major vessels were treated by enucleation because it was too difficult or dangerous to remove enough of the liver to obtain an adequate margin. A Pringle's maneuver usually was not performed during hepatic resection. In cases of blood loss of >500 mL during transection, we performed Pringle's maneuver with an ischemic time of 15 minutes and reflow time of 5 minutes.

The transection was performed with the CUSA, and the vessel coagulation was performed by the bipolar sealer (Aquamantys 2.3 Bipolar Sealer; Salient Surgical Technologies, Portsmouth, NH; Fig 1) or BC (Fig 2) according to the randomization process, to which the surgeon was not blinded. This device delivers RF energy to bleeding tissues via the use of a conductive saline fluid that increases the affected surface area during hemostasis and maintains a relatively cool surface temperature of approximately 100°C.[10] The thermal effect of the RF energy shrinks type I and III collagen fibers in the walls of arteries and veins, which serves as the mechanism to minimize perioperative bleeding.[10]

The surgeon maintained full control of saline flow by an electronic switch. Vessels thicker than 2 mm were ligated with thin (3/4–0) sutures in both groups. A closed-suction silicon drain was inserted into the subphrenic or subhepatic space close to the cut surface of the liver before abdominal wound closure. The drain was brought through a separate stab wound on the anterior abdominal wall and connected to a closed system with low suction pressure. The abdominal drain was removed on postoperative day 3, unless there was excessive leakage of ascites or bile. The study protocol was explained to all patients, and they understood that they would be selected randomly to undergo hepatic resection via CUSA with a bipolar sealer or with BC. All patients provided written informed consent to participate in the trial and were randomized by the envelope method. All operations were performed by the same surgeon, who had experience with more than 700 hepatic resections. The protocol for this study was approved by the institutional ethics committee.

Outcome measures. The primary end points were blood loss during parenchymal transection

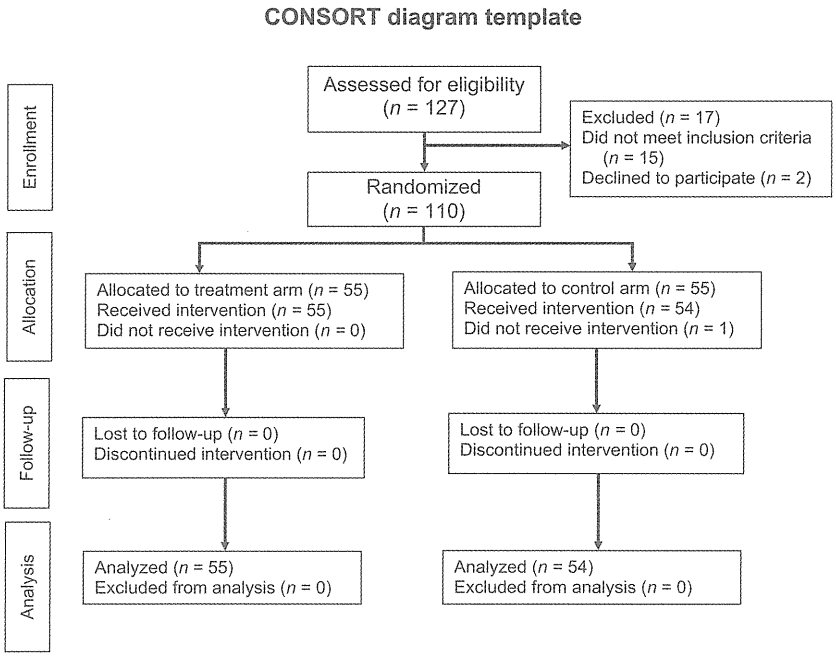

Fig 1. CONSORT diagram for this study.

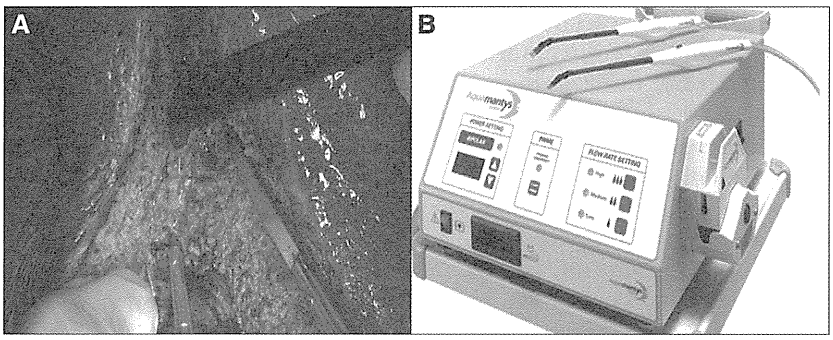

Fig 2. (*A*) Photograph showing transection of the liver using the CUSA and bipolar sealer. (*B*) Aquamantys RF bipolar sealer device.

Fig 3. Photograph showing transection of the liver using the CUSA and BC.

and speed of resection. Blood loss was carefully monitored before, during, and after liver transection. The amount of blood loss was estimated by inclusion of the suction volume after subtraction of rinsed fluids and weighing of the swabs that were used during transection. As soon as liver resection was completed, sterile paper was applied to the remaining liver surface, and the outline of the cut surface was drawn onto this paper to measure the surface area.

The secondary end point was the incidence of postoperative morbidity. Postoperative complications were defined and classified by the modified Clavien system.[18] To summarize, Grade I was any deviation from the normal postoperative course

Table I. Demographic, clinical, and pathologic characteristics of the 2 groups

	Bipolar cautery (n = *54*)	*Aquamantys bipolar sealer* (n = *55*)	P *value*
Age, y	71 ± 9	71 ± 10	.8700
Sex (male/female)	37/17	34/21	.4630
HBV/HCV/NBC/HBV + HCV	4/27/23/0	7/25/22/1	.5917
Diagnosis			.9176
Hepatocellular carcinoma	34 (63)	33 (60)	
Metastatic liver tumor	14 (26)	14 (25)	
Intrahepatic cholangiocarcinoma	3 (5)	5 (9)	
Benign disease	3 (5)	3 (5)	
Child-Pugh class (A/B)	46/8	46/9	.8237
ICGR15, %	11.8 ± 5.5	13.5 ± 4.8	.1192
Albumin, g/dL	3.9 ± 0.5	3.9 ± 0.4	.4226
Total bilirubin, mg/dL	0.7 ± 0.4	0.8 ± 0.3	.7391
Prothrombin time, %	93 ± 14	89 ± 13	.1936
Platelet count, $\times 10^4/\mu L$	20.8 ± 10.7	19.1 ± 9.4	.5987
AST, U/L	33 ± 23	41 ± 24	.1127
ALT, U/L	30 ± 32	39 ± 29	.1471
Operative procedure			.4358
Extended hemihepatectomy	4 (7)	5 (9)	
Hemihepatectomy	9 (17)	16 (29)	
Sectionectomy	27 (50)	22 (40)	
Segmentectomy	4 (7)	4 (7)	
Limited resection	10 (19)	8 (15)	
Tumor size, cm	3.2 ± 2.1	3.9 ± 2.7	.1911
Tumor number	1.4 ± 0.8	1.4 ± 0.7	.9915
Associated liver disease			.9785
Normal	18 (33)	18 (33)	
Fibrosis or hepatitis	27 (50)	27 (49)	
Cirrhosis	9 (17)	10 (18)	

Values in parentheses are percentages. Data represent the mean ± SD or the number of patients. Continuous data are mean ± SD.
ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *ICGR15*, indocyanine green retention rate at 15 min; *NBC*, nonhepatitis B or C virus.

that did not require special treatment, Grade II was a deviation that required pharmacologic treatment, Grade III required operative or radiologic 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 bile leakage was diagnosed by the following findings: detection of bile from the wound or the drain (total bilirubin level in the drain fluid >3 times that in the serum), intra-abdominal accumulation of bile confirmed by drainage, or demonstration of bile leakage on postoperative cholangiography.

Statistical analysis. In our recent experience, a mean blood loss of 990 mL with an SD of 510 mL was expected. To validate the hypothesis that the bipolar sealer could reduce blood loss by 300 mL with an α error of 0.05 and a β error of 0.20, a required sample size of 47 patients per group was calculated. Allowing for a dropout rate of 10% after randomization, we concluded that at least 52 patients were needed in each group. Results are expressed as mean ± SD. Demographic, physiologic, and clinical data for the 2 groups were compared by the *t*-test or the Mann-Whitney *U* test for continuous variables, whereas the χ^2 test or Fisher exact test was used for categorical data.

RESULTS

A total of 119 patients were assessed for eligibility for this study (Fig 3). Fifteen patients did not meet the inclusion criteria for the following reasons: bowel/bile duct resection,[3] repeat hepatectomy,[6] portal vein thrombus or previous portal vein embolization,[3] ruptured HCC,[2] and anticipated vascular resection.[1] Two patients declined to participate. Fifty-five patients were randomized to undergo treatment with the CUSA with the bipolar sealer, and 54 were randomized to undergo treatment with the CUSA with BC. Table I summarizes the baseline and operative characteristics. The 2 groups were well matched for all studied parameters that may represent risk factors for adverse outcomes.

Table II. Operative outcomes of the 2 groups

	Bipolar cautery (n = *54*)	*Aquamantys bipolar sealer* (n = *55*)	P *value*
Operation time, min	409 ± 148	382 ± 115	.3098
Total blood loss, mL	1076 ± 762	677 ± 433	.0486
Blood transfusion, ±	10/44	3/52	.0354
Resection area, cm^2	71 ± 42	75 ±52	.5501
Transection time, min	115 ± 65	81 ± 42	.0025
Blood loss during transection, mL	697 ±837	271 ± 233	.0079
Speed of transection, cm^2/min	0.52 ± 0.34	0.88 ± 0.46	<.0001
Blood loss/resection area, mL/cm^2	10.6 ± 9.1	4.9 ± 5.8	.0008
Number of ties	22.8 ± 11.1	13.1 ± 7.8	<.0001
Number of ties/resection area, /cm^2	0.54 ± 0.31	0.23 ± 0.15	<.0001
Number of patients who underwent Pringle's maneuver	14	11	.4619
Morbidity, ±	5/49	3/52	.4463
Bile leakage	3	0	
Intra-abdominal abscess	1	0	
Liver failure	0	0	
Pleural effusion and/or ascites	1	2	
Pneumonia	0	1	
Grade of operative complications			
I	0	0	.4105
II	0	1 (33%)	
IIIa	3 (60%)	2 (66%)	
IIIb	1 (20%)	0	
IVa	1 (20%)	0	
IVb	0	0	
V	0	0	
Postoperative hospital stay, d	17.1 ± 13.1	12.1 ± 6.5	.2492

Data represent the mean ± SD or the number of patients.

Operative outcomes for both groups are listed in Table II. There were no statistically significant differences between the 2 groups in the operation time, resection area, or number of patients who underwent Pringle's maneuver. Total blood loss, blood loss during transection, and blood loss divided by resection area were lesser in the bipolar sealer than in the BC group ($P = .0486$, .0079, and .0008, respectively). The requirement for blood transfusion was lesser in the bipolar sealer group ($P = .0354$). The transection time was lesser in the bipolar sealer group ($P = .0025$), and the speed of transection was faster ($P < .0001$). Moreover, fewer ties and ties divided by resection area were required during transection in the bipolar sealer than in the BC group ($P < .0001$). Postoperative morbidity and hospital stay were similar between groups, as were local recurrences at a mean follow-up of 14 months (median, 14; range, 7–24) and 13 months (median, 14; range, 7–24).

Postoperative peak values of serum aspartate aminotransferase were 355 ± 209 IU/L and 349 ± 220 IU/L in the BC and bipolar sealer groups, respectively, and those of serum alanine aminotransferase were 297 ± 206 IU/L and 283 ± 192 IU/L in the BC and bipolar sealer groups, respectively. Peak transaminase levels occurred on the first or second postoperative day in most cases, but there was no difference between the 2 groups. Similarly, there was no difference between the 2 groups in the postoperative peak levels of total serum bilirubin (2.2 ± 1.0 mg/dL vs 2.1 ± 1.0 mg/dL), lactate dehydrogenase (575 ± 207 IU/L vs 549 ± 262 IU/L), C-reactive protein (14.2 ± 8.4 mg/dL vs 11.7 ± 6.4 mg/dL), white blood cells (11,600 ± 4,300/mm^3 vs 11,700 ± 3,300/mm^3), nor minimum hemoglobin level (10.2 ± 1.7 g/dL vs 10.8 ± 1.5 g/dL). The minimum albumin level (2.5 ± 0.4 g/dL vs 2.7 ± 0.3 g/dL), prothrombin time (61 ± 14% vs 62 ± 10%), and platelet level (10.6 ± 5.0 × 10^4/mm^3 vs 11.3 ± 8.5 × 10^4/mm^3) were also similar between the 2 groups. The cost of the BC and bipolar sealer devices was 650 and 310 USD. Although repeated use of BC is possible, the bipolar sealer is disposable.

DISCUSSION

Excessive intraoperative blood loss and the possible requirement for blood transfusion are

major problems in hepatic resection for HCC or colorectal liver metastases.[19-21] Reduction of blood loss is one of the goals in liver operations, and several technical developments have been introduced for this purpose, including the Pringle maneuver[22] and selective vascular occlusion,[23] among other techniques. Regarding operative devices, CUSA has contributed to safe hepatectomy by making it easy to identify the vessels during parenchymal transection,[4] but it has no function in tissue sealing, and meticulous ligation is required to avoid bleeding or bile leakage from the cut surface of the liver. Thus, establishment of rapid hemostasis is critical. The current findings suggest that treatment with a bipolar sealer can decrease effectively total blood loss, intraoperative blood loss during hepatic parenchymal dissection, and the need for transfusion. These results corroborate and extend those of previous studies reporting the successful use of this technology during adolescent idiopathic scoliosis, primary total hip arthroplasty, or orthopedic joint reconstruction.[10,12-14,24,25]

The bipolar sealer reportedly seals blood vessels in soft tissue and cut bone while keeping the surface temperature at <100°C.[10] This device works by coupling RF energy from a standard electrosurgical generator with saline irrigation to conduct thermal energy. The thermal effect shrinks the collagen in the walls of veins and arteries, effectively stopping bleeding and oozing from the vessels without producing smoke or charring or burning tissue. The saline coupling of the bipolar sealer technology provides an advantage over conventional electrocautery for sealing cancellous tissue. This coupling provides a direct conduit between the electrodes and the embedded vessels, resulting in a rapid energy transfer. Furthermore, the depth of necrosis is minimal (<0.3 mm at 6 weeks and none at 12 weeks), allowing native blood vessels to assist with bone healing.[10] Collagen types I and III are known to shrink when heated and are abundant in the walls of blood vessels; the dry weight of veins and arteries is 58% and 28% collagen, respectively.[26] Connective tissue rich in type I collagen, such as that found in bone and articular cartilage, can shrink to about 60% its original size when heated to at least 60°C.[27,28] Hemostasis via vessel shrinking occurs without the tissue desiccation, smoking, and charring of conventional electrocautery.

In previous studies authors reported that the use of the RF coagulator TissueLink is associated with deep tissue coagulation and considerable liver necrosis in both human[29] and animal[30] studies. However, the present study demonstrated that the degree of liver injury was similar in the 2 groups.

Bile leakage is a particular concern in liver transection and can prolong the patient's hospital stay. Lupo et al[31] reported an increased incidence of biliary fistula after using RF, but all bile leakage occurred in the BC group. The bipolar sealer, with its sealing effect, also seemed effective in preventing bile leakage from the cut surface of the liver. The bipolar sealer is easy to handle and can seal tissues broadly, including relatively large vessels and bile ducts. According to our study, the bipolar sealer seemed to prevent bile leakage without ligation in ducts up to 4 mm in size.

In conclusion, the introduction of a bipolar sealer with CUSA resulted in decreases in excessive blood loss overall and increased speed in transection time with no increase in morbidity compared with standard bipolar cautery with CUSA during hepatectomy.

REFERENCES

1. Navarra G, Spalding D, Zacharoulis D, et al. Bloodless hepatectomy technique. HPB Surg 2002;4:95-7.
2. Torzilli G, Makuuchi M, Midorikawa Y, et al. Liver resection without total vascular exclusion: hazardous or beneficial? An analysis of our experience. Ann Surg 2001;233:167-75.
3. Romano F, Franciosi C, Caprotti R, et al. Hepatic surgery using the Ligasure vessel sealing system. World J Surg 2005;29:110-2.
4. Yamamoto Y, Ikai I, Kume M, et al. New simple technique for hepatic parenchymal resection using a Cavitron ultrasonic surgical aspirator and bipolar cautery equipped with channel for water dripping. World J Surg 1999;23: 1032-7.
5. Fasulo F, Giori A, Fissi S, et al. Cavitron Ultrasonic Surgical Aspirator (CUSA) in liver resection. Int Surg 1992;77:64-6.
6. Takatsuki M, Eguchi S, Yamanouchi K, et al. Two-surgeon technique using saline-linked electric cautery and ultrasonic surgical aspirator in living donor hepatectomy: its safety and efficacy. Am J Surg 2009;197:e27-9.
7. Lesurtel M, Selzner M, Petrowsky H, et al. How should transection of the liver be performed? A prospective randomized study in 100 consecutive patients comparing four different transection strategies. Ann Surg 2005;242:814-22.
8. Arita J, Hasegawa K, Kokudo N. Randomized clinical trial of the effect of a saline-linked radiofrequency coagulator on blood loss during hepatic resection. Br J Surg 2005;92: 954-9.
9. Takayama T, Makuuchi M, Kubota K, et al. Randomized comparison of ultrasonic vs clamp transection of the liver. Arch Surg 2001;136:922-8.
10. Marulanda GA, Ulrich SD, Seyler TM, et al. Reductions in blood loss with a bipolar sealer in total hip arthroplasty. Expert Rev Med Devices 2008;5:125-31.
11. Siegel HJ, Sparks DR, Casillas MA, et al. The use of bipolar hemosealing technology in orthopedic oncology: safety and clinical impact. Orthopedics 2008;31:10.
12. Marulanda GA, Krebs VE, Bierbaum BE, et al. Hemostasis using a bipolar sealer in primary unilateral total knee arthroplasty. Am J Orthop (Belle Mead NJ) 2009;38:E179-83.

13. Rosenberg AG. Reducing blood loss in total joint surgery with a saline-coupled bipolar sealing technology. J Arthroplasty 2007;22:82-5.
14. Samdani AF, Torre-Healy A, Asghar J, et al. Strategies to reduce blood loss during posterior spinal fusion for neuromuscular scoliosis: a review of current techniques and experience with a unique bipolar electrocautery device. Surg Technol Int 2008;17:243-8.
15. Yim AP, Rendina EA, Hazelrigg SR, et al. A new technological approach to nonanatomical pulmonary resection: saline enhanced thermal sealing. Ann Thorac Surg 2002; 74:1671-6.
16. Strasberg SM, Belghiti J, Clavn P-A, et al. The Brisbane 2000 terminology of liver anatomy and resection. Terminology Committee of the International Hepato-Pancreato-Biliary Association. HPB 2000;2:333-9.
17. Couinaud C, editor. "Le Foie: Etudes Anatomiques et Chirurgicales." Paris: Masson; 1957.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
19. Katz SC, Shia J, Liau KH, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg 2009;249:617-23.
20. Sima CS, Jarnagin WR, Fong Y, et al. Predicting the risk of perioperative transfusion for patients undergoing elective hepatectomy. Ann Surg 2009;250:914-21.
21. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240:698-708.
22. Imamura H, Takayama T, Sugawara Y, et al. Pringle's maneuver in living donors. Lancet 2002;360:2049-50.
23. Malassagne B, Cherqui D, Alon R, et al. Safety of selective vascular clamping for major hepatectomies. J Am Coll Surg 1998;187:482-6.
24. Mankin KP, Moore CA, Miller LE, et al. Hemostasis with a bipolar sealer during surgical correction of adolescent idiopathic scoliosis. J Spinal Disord Tech 2012;25:259-63.
25. Zeh A, Messer J, Davis J, et al. The Aquamantys system—an alternative to reduce blood loss in primary total hip arthroplasty? J Arthroplasty 2010;25:1072-7.
26. Gorisch W, Boergen KP. Heat-induced contraction of blood vessels. Lasers Surg Med 1982;2:1-13.
27. Chen SS, Wright NT, Humphrey JD. Heat-induced changes in the mechanics of a collagenous tissue: isothermal, isotonic shrinkage. J Biomech Eng 1998;120:382-8.
28. Wallance AL, Hollinshead RM, Frank CB. The scientific basis of thermal capsular shrinkage. J Shoulder Elbow Surg 2000;9:354-60.
29. Poon RT, Fan ST, Wong J. Liver resection using a saline-linked radiofrequency dissecting sealer for transection of the liver. J Am Coll Surg 2005;200:308-13.
30. Topp SA, McClurken M, Lipson D, et al. Saline-linked surface radiofrequency ablation: factors affecting steam popping and depth of injury in the pig liver. Ann Surg 2004;239:518-27.
31. Lupo L, Gallerani A, Panzera P, et al. Randomized clinical trial of radiofrequency-assisted versus clamp-crushing liver resection. Br J Surg 2007;94:287-91.

Kaibori et al. BMC Gastroenterology 2013, 13:119
http://www.biomedcentral.com/1471-230X/13/119

BMC Gastroenterology

RESEARCH ARTICLE Open Access

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 non-anatomical 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 ($\times 10^4$/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).

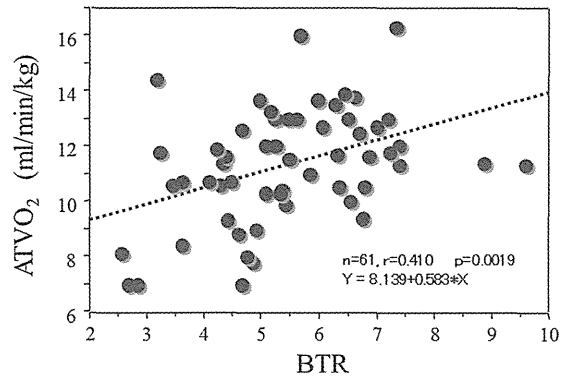

Figure 1 Relationships between preoperative BTR and AT VO_2 in HCC patients. There was a significant correlation between BTR and AT VO_2 (r = 0.410, Y = 8.139 + 0.583 * X, $p = 0.0019$). *BTR* branched chain amino acid/tyrosine ratio, *AT VO_2* anaerobic threshold oxygen consumption.

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

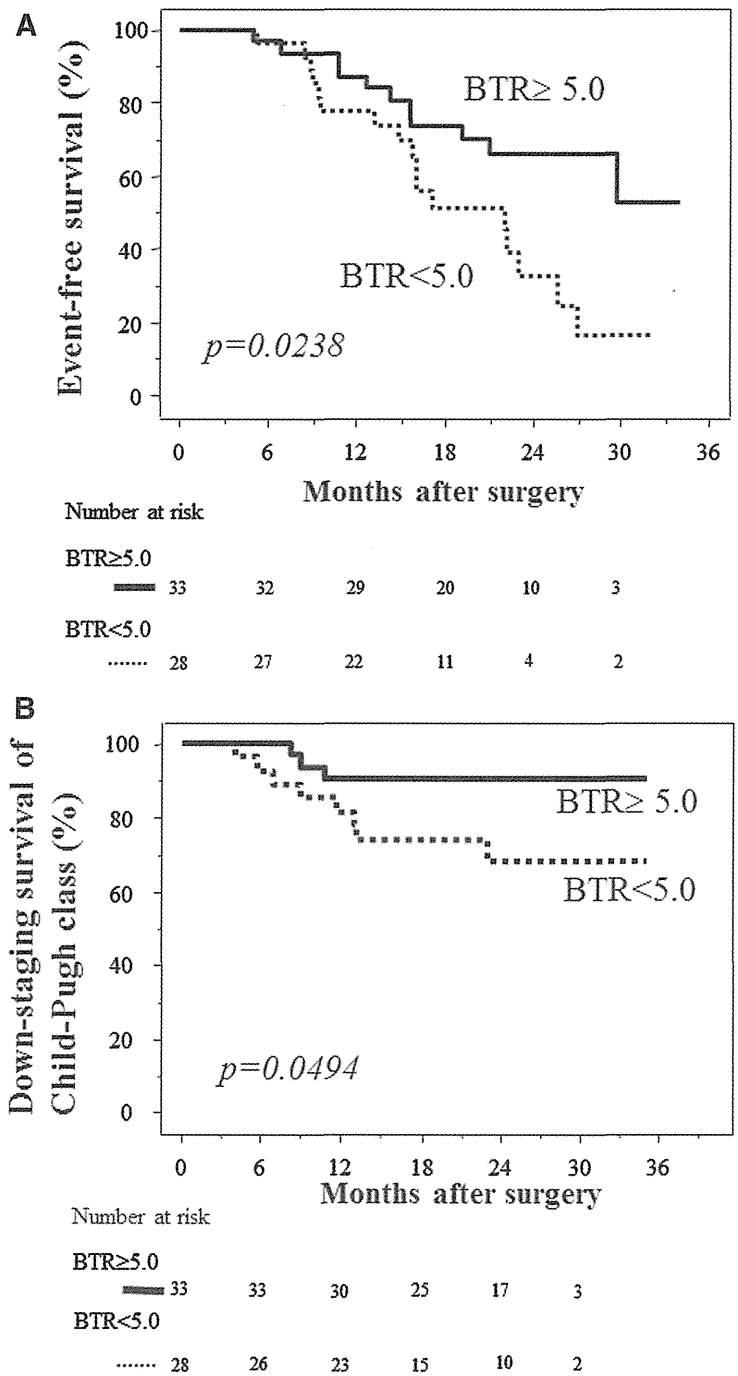

Figure 2 Comparisons of event-free survival and maintenance of Child-Pugh class after hepatectomy between patients with preoperative BTR ≥5.0 and <5.0. (A) Event-free survival. The survival rate was significantly higher in patients with preoperative BTR ≥5.0 (solid line) than BTR <5.0 (dotted line) ($p = 0.0238$). **(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.

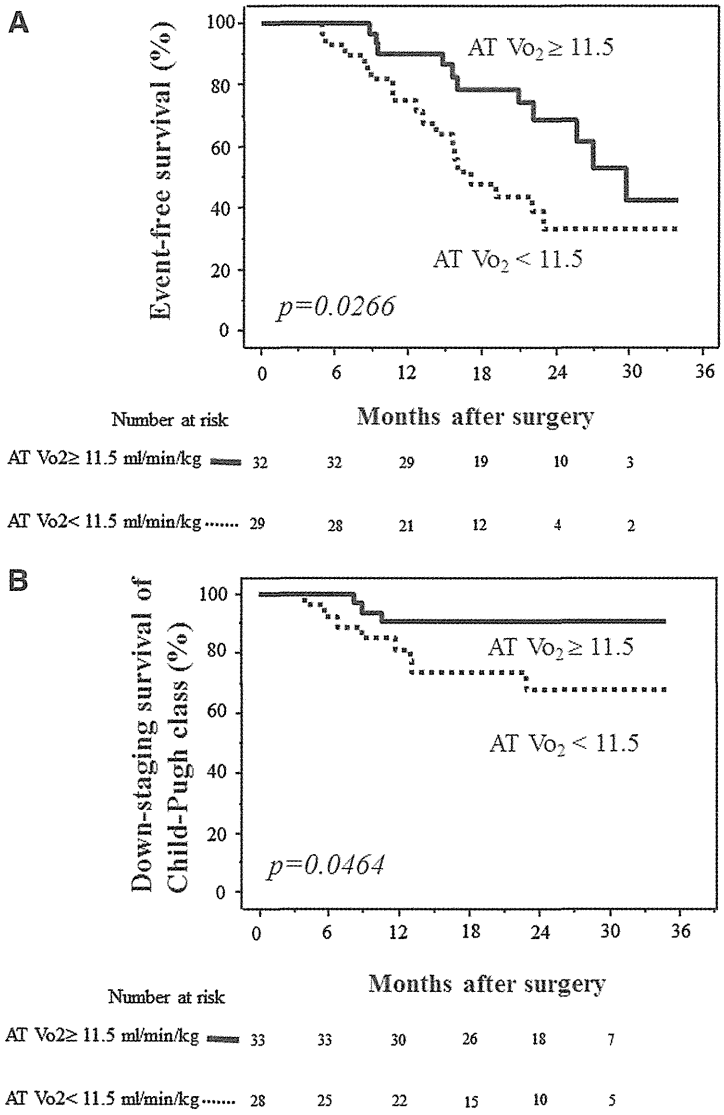

Figure 3 Comparisons of event-free survival and maintenance of Child-Pugh class after hepatectomy between patients with preoperative AT VO_2 ≥11.5 ml/min/kg and <11.5 ml/min/kg. (A) Event-free survival. The survival rate was significantly higher in patients with preoperative AT VO_2 ≥11.5 ml/min/kg (solid 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.

Acknowledgements
This work was supported in part by Grants-in-Aid from the Ministry of Health, Labor, and Welfare of Japan.

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.

Received: 30 August 2012 Accepted: 19 July 2013
Published: 22 July 2013

References
1. Older P, Smith R: **Experience with the preoperative invasive measurement of haemodynamic, respiratory and renal function in 100 elderly patients scheduled for major abdominal surgery.** *Anaesth Intensive Care* 1988, **16:**389–395.
2. Halm EA, Browner WS, Tubau JF, Tateo IM, Mangano DT, Study of Perioperative Ischemia Reserch Group: **Echocardiography for assessing cardiac risk in patients having noncardiac surgery.** *Ann Intern Med* 1996, **125:**433–441.
3. Dunselman PH, Kuntze CE, Van Bruggen A, *et al*: **Value of New York Herat Association classification, radionuclide ventriculography, and cardiopulmonary exercise tests for selection of patients for congestive heart failure studies.** *Am Heart J* 1988, **116:**1475–1482.
4. Mangano DT, London MJ, Tubau JF, Study of Perioperative Ischemia Reserch Group, *et al*: **Dipyridamole thallium-201scintigraphy as a preoperative screening test: a reexamination of its predictive potential.** *Circulation* 1991, **84:**493–502.
5. Reilly DF, McNeely MJ, Doerner D, *et al*: **Self-reported exercise tolerance and the risk of serious perioperative complications.** *Arch Intern Med* 1999, **159:**2185–2192.
6. Girish M, Trayner E Jr, Dammann O, Pinto-Plata V, Celli B: **Symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications after high-risk surgery.** *Chest* 2001, **120:**1147–1151.
7. Older P, Hall A, Hader R: **Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly.** *Chest* 1999, **116:**355–362.
8. Older P, Smith R, Courtney P, Hone R: **Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing.** *Chest* 1993, **104:**701–704.
9. Bosch X, Ribes J, Borras J: **Epidemiology of primary liver cancer.** *Semin Liver Dis* 1999, **19:**271–285.
10. Ziegler TR: **Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma.** *JPEN J Parenter Enteral Nutr* 1996, **20:**91–92.
11. Ishikawa Y, Yoshida H, Mamada Y, *et al*: **Prospective randomized controlled study of short-term perioperative oral nutrition with branched chain amino acids in patients undergoing liver surgery.** *Hepatogastroenterology* 2010, **57**(99–100):583–590.
12. Beaver WL, Wasserman K, Whipp BJ: **Bicarbonate buffering of lactic acid generated during exercise.** *J Appl Phsiol* 1986, **60:**472–478.
13. Whipp BJ, Wasserman K: **Oxygen uptake kinetics for various intensities of constant-load work.** *J Appl Physiol* 1972, **33:**351–356.
14. Wasserman K, Hansen JE, Sue DY: **Principles of exercise testing and interpretation.** In *Measurement of the physiological response to exercise.* Edited by Wasserman K, Hansen JE, Sue DY, Whipp BJ. Philadelphia, PA: Lea and Febiger; 1987:27–46.
15. Snowden CP, Prentis JM, Anderson HL, *et al*: **Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery.** *Ann Surg* 2010, **251:**535–541.
16. Coin A, Sergi G, Minicuci N, *et al*: **Fat-free mass and fat mass reference values by dual-energy X-ray absorptiometry (DEXA) in a 20-80 year-old Italian population.** *Clin Nutr* 2008, **27:**87–94.
17. Lehnert ME, Clarke DD, Gibbons JG, *et al*: **Estimation ofbody water compartments in cirrhosis by multiplefrequency bioelectrical-impedance analysis.** *Nutrition* 2001, **17:**31–34.
18. Strasberg SM, Belghiti J, Clavien PA, *et al*: **The Brisbane 2000 terminology of liver anatomy and resection: terminology committee of the International Hepato-Pancreato-Biliary Association.** *HPB* 2000, **2:**333–339.
19. Couinaud C (Ed): *"Le Foie: Etudes Anatomiques et Chirurgicales".* Paris: Masson; 1957.
20. Dindo D, Demartines N, Clavien PA: **Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.** *Ann Surg* 2004, **240:**205–213.
21. Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T: **Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus.** *J Thorac Cardiovasc Surg* 2001, **121:**1064–1068.
22. Win T, Jackson A, Sharples L, *et al*: **Cardiopulmonary exercise tests and lung cancer surgical outcome.** *Chest* 2005, **127:**1159–1165.
23. Nagamatsu Y, Terazaki Y, Muta F, Yamana H, Shirouzu K, Ishitake T: **Expired gas analysis during exercise testing pre-pneumonectomy.** *Surg Today* 2005, **35:**1021–1025.
24. Smith TP, Kinasewitz GT, Tucker WY, Spillers WP, George RB: **Exercise capacity as a predictor of post-thoracotomy morbidity.** *Am Rev Respir Dis* 1984, **129:**730–734.
25. Bechard D, Wetstein L: **Assessment of exercise oxygen consumption as preoperative criterion for lung resection.** *Ann Thorac Surg* 1987, **44:**344–349.
26. Bolliger CT, Soler M, Stulz P, *et al*: **Evaluation of high-risk lung resection candidates, pulmonary haemodynamics versus exercise testing: a series of five patients.** *Respiration* 1994, **61:**181–186.
27. Weisman IM: **Cardiopulmonary exercise testing in the preoperative assessment for lung resection surgery.** *Semin Thorac Cardiovasc Surg* 2001, **13:**116–125.

28. Avramoglu RK, Basciano H, Adeli K: **Lipid and lipoprotein dysregulation in insulin resitant states.** *Clin Chim Acta* 2006, **368**:1–19.
29. Furukawa S, Fujita T, Shimabukuro M, *et al*: **Increased oxidative stress in obesity and its impact on metabolic syndrome.** *J Clin Invest* 2004, **114**:1752–1761.
30. Valgimigli M, Valgimigli L, Trere D, *et al*: **Oxidative stress EPR measurement in human liver by radical-probe technique: correlation with etiology, histology and cell proliferation.** *Free Radic Res* 2002, **36**:939–948.
31. Powell EE, Jonsson JR, Clouston AD: **Steatosis: co-factor in other liver diseases.** *Hepatology* 2005, **42**:5–13.
32. Hickman IJ, Jonsson JR, Prins JB, *et al*: **Modest weight loss and physical activity in overweight patients with chronoc liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life.** *Gut* 2004, **53**:413–419.
33. Moriwaki H, Miwa Y, Tajika M, Kato M, Fukushima H, Shiraki M: **Branched-chain amino acids as a protein- and energy-source in liver cirrhosis.** *Biochem Biophys Res Commun* 2004, **313**:405–409.
34. Fisher JE, Rosen HM, Ebeid AM, James JH, Keane JM, Soeters PB: **The effect of normalization of plasma amino acids on hepatic encephalopathy in man.** *Surgery* 1976, **80**:77–91.
35. Azuma Y, Maekawa M, Kuwabara Y, Nakajima T, Taniguchi K, Kanno T: **Determination of branched-chain amino acids and tyrosine in serum of patients with various hepatic diseases, and its clinical usefulness.** *Clin Chem* 1989, **35**:1399–1403.
36. Shimizu H, Taniguchi K, Sugiyama M, Kanno T: **Rapid enzymatic analysis of plasma for tyrosine.** *Clin Chem* 1990, **36**:32–35.
37. Mizuguchi T, Kawamoto M, Meguro M, Nakamura Y, Harada K, Kukita K, Hirata K: **Prognostic impact of preoperative the branched-chain amino acid to the tyrosine ratio in hepatocellular carcinoma patients after initial hepatectomy.** *J Gastrointest Surg* 2011, **15**:1433–1439.

doi:10.1186/1471-230X-13-119
Cite this article as: Kaibori *et al.*: Assessment of preoperative exercise capacity in hepatocellular carcinoma patients with chronic liver injury undergoing hepatectomy. *BMC Gastroenterology* 2013 **13**:119.

J Gastrointest Surg (2013) 17:1422–1428
DOI 10.1007/s11605-013-2262-x

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

Received: 31 January 2013 / Accepted: 12 June 2013 / Published online: 25 June 2013

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