to excess hormones, they often go unnoticed until they are in the advanced stages. Previously, NF-pNETs were often detected as larger tumors that were accompanied by nonspecific pressure symptoms, such as abdominal pain or discomfort; abdominal distension; or a palpable mass in advanced stages with distant metastasis or local invasion. The number of NF-pNETs that have been incidentally detected has increased due to the advances in diagnostic imaging over the last few decades. Compared with other pancreatic tumors, pNETs progress slowly and are associated with a better prognosis. However, they have malignant potential, including local invasion, lymph node metastasis, or distant metastasis. More than half of NF-pNETs are malignant[3,13]. Therefore, most recommendations favor surgical resection for all patients, even for small NF-pNETs[4].

Numerous retrospective studies have previously examined the poor prognosis for NF-pNETs[6,7,14-21]. According to these studies, the predictors of the prognosis for NF-pNETs include the presence of liver metastases and incomplete resection of the tumor.

Several studies have indicated that lymph node metastasis is a poor prognostic factor[5-9]. In addition, Boninsegna *et al*[8] reported that lymph node metastasis is a prognostic factor for the recurrence of malignant pNETs after curative surgery. If malignancy of the tumor or lymph node metastasis is suspected, pancreatic resection with the addition of lymphadenectomy is recommended. It is often difficult to judge preoperatively whether a tumor is benign or malignant, except in patients with distant metastases or local invasion.

The tumor size appears to correlate with the malignant potential of NF-pNETs. Bettini *et al*[2] reported that the chance of malignancy significantly increases when the size of NF-pNETs exceeds 20 mm. A Japanese epidemiological study also found a significant correlation between NF-pNETs that exceed 20 mm in diameter and the presence of distant metastases[3]. Pancreatic resection and prophylactic regional lymphadenectomy are recommended for treating possible malignancy when the tumors exceed 20 mm in diameter[4]. However, several studies have failed to identify a correlation between the tumor size and prognosis[5,13,22,23], and other studies have demonstrated that even tumors smaller than 10 mm can be malignant[24,25]. Therefore, surgical resection is recommended even in small tumors.

Currently, the association between the tumor size and the incidence of lymph node metastasis is controversial. Hashim *et al*[9] reported that there is an increased probability of nodal metastasis when the tumor size is larger than 15 mm. Tsutsumi *et al*[26] reported an increased prevalence of lymph node metastasis in patients with gastrinomas and non-gastrinoma who have tumor sizes of 15 mm or larger. In contrast, Parekh *et al*[27] reported that the tumor size is not associated with lymph node metastasis. A number of studies have reported that the incidences of lymph node metastases for patients with NF-pNETs smaller than 20 mm and 15 mm are 14.4% and 8%, respectively[2,9,26-29]. Over the last few decades, the number of NF-pNETs that are incidentally detected with diagnostic imaging has increased, and compared with symptomatic NF-pNETs, tumors that are incidentally detected have a good prognosis and low risk of malignancy[2,21].

In the present study, one of the 9 patients was diagnosed with von Hippel-Lindau disease, and this patient should be considered separately because the biological properties of sporadic pNETs and hereditary pNETs, such as MEN-1 and von Hippel-Lindau disease, are different with respect to the incidence, number of tumors, and prognosis. One of the 8 patients with sporadic NF-pNETs had NEC with a tumor size of 22 mm. Except for the case with NEC, the direct invasion and metastasis to the lymph nodes was only observed in a relatively large tumor with a diameter size of 32 mm. Tumors smaller than 10 mm in diameter showed no signs of malignancy, were well differentiated, and lacked lymph node metastasis. Additionally, none of the cases had recurrence, including in the lymph nodes or direct metastasis, for more than 10 years after surgery. Lymphadenectomy may be omitted in the future after further investigation of a large number of small NF-pNETs. However, Hashim *et al*[9] reported that even tumors smaller than 10 mm metastasize at a rate of 12%. Additionally, lymphadenectomy is often omitted for small pNETs that are larger than 10 mm in size; the possibility of lymph node metastasis may be underestimated in those cases. Omission of lymphadenectomy needs to be carefully considered with further study. Even when lymphadenectomy is omitted, long-term follow-up is essential because there is a risk of late recurrence. If malignancy is confirmed postoperatively, oncologically appropriate lymphadenectomy must be considered based on the factors that determine the malignant potential, such as the Ki67 index, tumor differentiation status, surgical margin, and vascular invasion such as lymphoductal, neural, and venous[19,20].

In the present study, CgA, PP, and other hormones were not measured; it is important to measure these hormones to identify recurrences during follow-up.

The present study is limited by its small sample size, single institution bias, and retrospective nature. In the future, a larger number of patients at multiple centers should be studied.

In summary, we found that small NF-pNETs tend to have less malignant potential. In the present study, six of 7 cases of sporadic NF-pNETs, except for a case with NEC, were small tumors (smaller than 10 mm diameter). These small tumors showed no evidence of malignancy, were well differentiated, and lacked lymph node metastasis. This finding indicates that lymphadenectomy may be omitted in the future for small NF-pNETs, particularly for those tumors that are incidentally detected after further investigation. When lymphadenectomy is omitted, long-term follow-up is essential, and additional resection should be considered if malignancy is confirmed postoperatively. The tumor size can easily be measured pre-

operatively, and further study is expected to find other factors for predicting the malignant potential of small NF-pNETs.

COMMENTS

Background

Even small NF-Pancreatic neuroendocrine tumors (pNETs) have malignant potential and may spread to lymph nodes or metastasize to distant sites. Therefore, oncologic resection with regional lymphadenectomy is currently recommended. Increasingly smaller NF-pNETs are being identified with improved and more frequent radiological imaging. However, because the clinicopathological features of extremely small NF-pNETs are not yet known, there are no standard criteria for performing a lymphadenectomy when small, asymptomatic NF-pNETs are identified.

Research frontiers

NF-pNETs have malignant potential and may spread to lymph nodes or metastasize to distant sites. However, the clinicopathological features of extremely small NF-pNETs are not yet known. In this study, the authors present their experience with the clinicopathological features of small NF-pNETs (diameters less than 10 mm).

Innovation and breakthroughs

Small NF-pNETs are being identified with improved and more frequent radiological imaging. However, few studies have examined small NF-pNETs with diameters less than 10 mm. In this study, tumors with diameters less than 10 mm showed no evidence of malignancy, were well differentiated, and lacked lymph node metastasis. Additionally, there were no recurrences after the operations, including in the lymph nodes or direct metastasis, for more than 10 years after surgery.

Applications

A previous study reported that the incidence of lymph metastasis is higher for larger tumors. Our findings indicate that lymphadenectomy of small NF-pNETs may be omitted in the future after further investigation of a large number of patients with small NF-pNETs.

Terminology

pNETs are relatively rare disease and progress slowly and are associated with a better prognosis. However, they have malignant potential, including local invasion, lymph node metastasis, or distant metastasis. pNETs are classified into functioning pNETs, which present with specific symptoms due to excess hormones, and nonfunctioning pNETs (NF-pNETs), which do not present with these symptoms.

Peer review

The present manuscript by Furukori *et al* focuses on the need of lymphadenectomy in NF-pNETs < 10 mm and suggests that in these tumors the lymphadenectomy can be omitted. The concept is very challenging.

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ELSEVIER

Establishment of Educational Program for Multiorgan Procurement From Deceased Donors

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ABSTRACT

Introduction. Multiorgan procurement is not an easy procedure and requires special technique and training. Since sufficient donors are not available for on-site training in Japan, establishment of the educational program for multiorgan procurement is mandatory.

Materials and methods. Development of e-learning and simulation using pigs are our main goals. E-learning contains three dimensional computer graphic (3DCG) animations of the multiorgan procurement, explanation of both donor criteria and procurement procedure, and self-assessment examination. To clarify the donor criteria, the risk factors to 3-month survival of the recipients were analyzed in 138 adult cases of liver transplantation. The 3DCG animation for liver procurement was developed, which was used in the lecture prior to the simulation on August 10, 2013. The results of the examination after this lecture (exam 2013) were compared with the results after the lecture without using animation in 2012 (exam 2012). The simulation was performed by 97 trainees divided into 9 teams, and the surveys were conducted.

Results. The risk factors for early outcome of the recipients were cold ischemia time ($\geq$10 hours), Model for End-stage Liver Disease score ($\geq$20), and donor age ($\geq$55 years). Results of examination showed that overall percentage of the correct answers was significantly higher in exam 2013 than in exam 2012 (48.3% vs 32.7%; $P = .0001$). The survey after the simulation of multiorgan procurement revealed that most trainees thought that the simulation was useful and should be continued.

Conclusion. The novel educational program could allow young surgeons to make precise assessments and perform the exact procedure in the multiorgan procurement.

ALTHOUGH the number of deceased donors slightly increased since 2010 when the organ transplantation law was revised, there is still a large mismatch between supply and demand of deceased donors in Japan. To maximize the organ utility, multiorgan procurement of 5 organs including heart, lung, liver, pancreas, and kidney from most donors has become routine. Multiorgan procurement, however, is not an easy procedure, and it requires

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special technique and training. Sufficient donors are not available to perform on-site training for young surgeons. To prepare for the demand of increasing numbers of deceased donors in future, it is necessary to establish an educational program to ensure safe and expert multiorgan procurement. Herein, we report the development of an educational program and its efficacy in training of the liver procurement.

MATERIALS AND METHODS

Development of e-learning and simulation using pigs for multiorgan procurement are our main goal to establish the educational program. E-learning contains three dimensional computer graphic (3DCG) animations of the multiorgan procurement, explanation of both donor criteria and procurement procedure, and self-assessment examination.

It is crucial to elucidate the standard criteria for exact assessment of donors. From 1999 to 2013, 185 cases of donor procurement were performed, of which 160 cases of liver grafts were used for transplantation. The 25 risk factors of donors were analyzed in 138 adult cases of liver transplantation. The donor factors included date of procurement, hospital of procurement, admission date, age, sex, height, weight, body mass index, cause of death, length of hospital stay, length of cardiopulmonary resuscitation (>10 minutes), history of smoking, history of drinking, hemoglobin A1c, serum Na, serum blood urea nitrogen, serum creatinine, serum glucose, serum total bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase, serum amylase, serum C-reactive protein, usage of high-dose dopamine (>15 mcg/kg/min), and usage of more than 2 vasopressors (from dopamine, dobutamine, noradrenalin, adrenalin, and vasopressin).

The 3DCG animation has been produced for liver and liver-pancreas procurement along with the scenario by Waseda University and Quality Experience Design Ltd, Tokyo. The solitary liver procurement procedure contained 2 sections: section A consisted of 11 sequences from opening the abdomen to cross-clamping the aorta, and section B consisted of 5 sequences from dissection of the common bile duct to procurement of the liver graft. The combined liver and pancreas procurement also contained 2 sections: section A (same as solitary liver procurement) and section C, which consisted of 10 sequences from mobilization of the duodenum to separation of liver from pancreas on the back table. The e-learning system was prepared to include 3DCG animations and explanation of both donor criteria and procurement procedure to educate a trainee prior to the simulation. This system will be open on the website for easy access to the trainees all across Japan.

Simulation for multiorgan procurement including heart, lung, liver, and pancreas was performed by each organ team in the Medical Innovation Institute of Technology Center, Johnson and Johnson, Inc. Japan (Sukagawa, Fukushima Prefecture, Japan) on August 10, 2013. The lectures for the procurement of each organ team were performed. The 3DCG animation was used for the liver procurement lecture. After that the self-assessment examination was performed.

A total of 41 trainees for liver procurement took the examination. The examination contained 7 questions related to both donor criteria and procurement of the liver; 4 questions (questions 1, 2, 5, 7) for complication asked the correct response to the donor status or complications during procurement procedure and 3 (questions 3,

Table 1. Contents of the Questions in Self-assessment Examination and Comparison of the Correct Answers Between Examinations in 2012 and in 2013

No.	QC	Questions	Answer Categories	Percentage of Correct Answers		*P*
				Exam 2012	Exam 2013	
1a	C	How would you respond when the blood pressure of the	Diagnosis	7.5	14.6	.259
1b		donor drops to 80/50 mm Hg under the dopamine drip at 5 μg/kg/min prior to the donor surgery?	Treatment	35.8	100.0	.0001
2a	C	How would you respond when you find a 3-cm diameter	Diagnosis	69.8	62.2	.215
2b		tumor on the surface of the liver during the donor surgery?	Treatment	22.6	24.4	.916
3a	A	How would you respond when you find the variant right	Procurement method	58.5	51.2	.314
3b		hepatic artery (the right hepatic artery from the superior mesenteric artery) under the circumstance that both liver and pancreas are planned to be procured?	Reconstruction method	32.1	61.0	.014
4a	A	How would you respond when you find the variant left	Procurement method	39.6	22.0	.023
4b		branch (the left hepatic artery from the left gastric artery) under the circumstance that both liver and pancreas are planned to be procured?	Reconstruction method	9.4	29.3	.022
5a	C	How would you respond when you get bleeding behind	Diagnosis	47.2	85.4	.0001
5b		the aorta during dissecting the abdominal aorta just above the bifurcation for cannulation?	Treatment	47.2	81.7	.002
6a	A	How would you respond when you find the variant renal	Place of cannulation	37.5	46.3	.644
6b		artery arising just above the aortic bifurcation during dissecting the abdominal aorta for cannulation?	Method of perfusion	12.5	19.5	.536
7a	C	How would you respond when you get bleeding behind	Method of hemostasis	27.5	31.7	.318
7b		the infraphrenic aorta during dissecting the aorta for cross-clamping?	Next step	40.0	48.8	.647
Total				34.8	48.4	.001

Abbreviations: QC, question category; C, complication; A, anatomy.

4, 6) for anatomy asked the correct response when you find an anatomical variation during procurement (Table 1). The result of the examination (exam 2013) was compared with the results after the lecture in 2012 (exam 2012) without using animation.

After demonstration of multiorgan procurement by the expert surgeons, the simulation for multiorgan procurement was performed by 97 trainees divided into 9 teams (each team consisted of approximately 10 young surgeons including 3 or 4 liver surgeons). After that, the survey was conducted.

Statistical analyses were performed with software SPSS version 21 (Japan IBM, Tokyo); univariate analysis with Fisher exact test and multivariate analysis with logistic regression analysis were used for risk factor analysis of donors, and t test was used for comparing examination results. P values less than .05 were considered statistically significant.

RESULTS

From the results from 138 cases of deceased donor liver transplantation in adults, 3 factors were independent for 3-month survival; cold ischemia time more than 10 hours (Exp (B) 61.3 (6.8–550.4), $P = .001$), Model for End-stage Liver Disease (MELD) score more than 20 (Exp (B) 4.9 (1.0–23.3), $P = .013$), and donor age more than 55 years (Exp (B) 6.0 (1.5–25.0), $P = .045$).

The results of the examinations showed that overall percentage of correct answers was significantly higher in exam 2013 than in exam 2012 (48.3% vs 32.7%; $P = .0001$; Table 1). While percentage of correct answers to the questions for complication was significantly higher in exam 2013 than in exam 2012 (54.5% vs 35.2%; $P = .0001$), there was no difference between exam 2013 and exam 2012 (36.0% vs 30.0%; $P = .271$) in percentage of the correct answers to the questions for anatomy.

Survey results from the 79 participants of the simulation of multiorgan procurement on August 10, 2013, showed participants in postgraduate 10 to 15 years were most predominant (37%), 52% of the participants could be operators in the any parts of the simulation, 94% agreed that the simulation was useful to improve their skills for procurement, 82% thought that they were prepared for real multiorgan procurement, 90% thought that they learned how to cooperate with other teams, and 99% thought that the simulation should be continued.

DISCUSSION

Three independent factors including cold ischemia time, MELD score, and donor age affected the early outcome in liver transplantation. Those were similar results compared to the one from earlier series of deceased donors [1]. Eliminating the recipients with high MELD score and elder donors is not practical. Minimizing cold ischemia time is the most certain and important method to improve early outcome. Close cooperation of the donor and recipient operations is critical to minimize cold ischemia time.

The results of the examination in 2013 improved significantly, compared to those in 2012, especially with the questions for complications. The 3DCG animation was used in the lecture prior to the simulation for the first time. The lecture with step-by-step explanation along with the animation and enriched contents of tips and pitfalls following each sequence of the animation can possibly be attributed to the improvement in the questions for complications in the 2013 examination. Instead, the explanation of anatomical variation was not sufficient because the animation was based on the regular anatomy in the limited time of the lecture. The e-learning has been prepared for the website and will be able to contain the enriched explanation for both complications and anatomical variations. A trainee could have enough time to study through e-learning and take the self-assessment examination prior to the simulation.

As apparent in the survey result, the simulation is one of the most important steps in the educational program to judge the self-assessment of surgical procedure as well as to learn how to cooperate with each other in multiorgan procurement. The survey results showed most of the participants thought that the simulation was useful. Financial support is the critical issue to continue the simulation. Either the government or hospitals registered for deceased donor transplantation should offer the sufficient support to maintain the quality of organ procurement in Japan.

In conclusion, the novel educational program could allow young surgeons to make precise assessment and perform the multiorgan procurement procedure. The establishment of this program could achieve safer donor operation, less graft failure, and better outcome of organ transplantation.

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RETROSPECTIVE STUDY

Hepatic clearance measured with ^{99m}Tc-GSA single-photon emission computed tomography to estimate liver fibrosis

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Abstract

AIM: To evaluate the clinical utility of hepatic clearance (HC) measured with technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography (SPECT) to estimate the degree of liver fibrosis.

METHODS: Seventy-eight consecutive patients who underwent initial hepatectomy due to hepatocellular carcinoma were enrolled in this study. Indocyanine green clearance (ICG R15), quantitative indices estimated by ^{99m}Tc-GSA [the receptor index (LHL15 and HH15) and HC *via* SPECT analysis], and conventional liver function tests were performed before hepatectomy. Correlations among the quantitative indices for liver functional reserve, conventional liver function tests, and the degree of liver fibrosis were evaluated.

RESULTS: The degree of liver fibrosis was correlated with ICG R15, HH15, LHL15, and HC. HC showed the best correlation with conventional liver function tests. According to multivariate analysis, HC and LHL15 were significant independent predictors of severe fibrosis. HC was the most valuable index for predicting severe fibrosis.

CONCLUSION: HC measured with ^{99m}Tc-GSA SPECT is a reliable index for assessing liver fibrosis before hepatectomy.

Key words: Fibrosis; Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin; Single-photon emission computed tomography; Hepatic clearance; Liver resection

Core tip: This retrospective study evaluated the clinical utility of hepatic clearance measured with technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography for estimating the degree of liver fibrosis. We demonstrated that ^{99m}Tc-GSA hepatic clearance showed strong correlations with the degree of liver fibrosis and conventional liver function tests. It is a reliable index for assessing severe liver fibrosis. We believe that this quantitative index can yield a more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

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INTRODUCTION

Liver fibrosis is a negative predictive factor for postoperative hepatic failure[1-3]. Cirrhosis is a well-known risk factor for postoperative hepatic failure[1,3,4]. Moreover, morbidity and mortality are high for patients with severe liver fibrosis undergoing liver resection[2,5,6]. Therefore, the accurate preoperative estimation of the extent of hepatic fibrosis is essential for successful liver surgery. Although many liver fibrosis indicators have been proposed for preoperative evaluation[7-10], the best indicator for evaluating liver fibrosis has not yet been established.

Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy reflects the liver functional reserve and is reported to correlate with several hepatic function tests[11,12]. However, few available analyses can determine the degree of liver fibrosis. Single-photon emission computed tomography (SPECT) analysis in ^{99m}Tc-GSA liver scintigraphy, which can evaluate GSA accumulation in the liver, was also developed to investigate liver function[13]. These analyses calculate hepatic clearance (HC) with the outline extraction method, using a program based on a radiopharmacokinetic model, as described by Shuke *et al*[14,15].

In this study, we investigate the contribution of HC measured with ^{99m}Tc-GSA SPECT to assess liver fibrosis.

MATERIALS AND METHODS

Patients

Between January 2011 and March 2014, 78 consecutive patients who underwent an initial hepatectomy due to hepatocellular carcinoma were enrolled in this study. The surgery was performed within 1 wk after ^{99m}Tc-GSA liver scintigraphy examination, and conventional tests were performed. All procedures were performed after informed consent was received from the patients and after approval from the Ethics Committee of Asahikawa Medical University Hospital was obtained. This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

^{99m}Tc-GSA liver scintigraphy and the receptor index

^{99m}Tc-GSA liver scintigraphy was scheduled for the patients on the day before their hepatectomy. ^{99m}Tc-GSA was supplied by Nihon Medi-Physics (Nishinomiya, Japan). After the intravenous injection of 185 MBq ^{99m}Tc-GSA, dynamic imaging was performed with the patient in the supine position. LHL15 was calculated by dividing the radioactivity of the region of interest (ROI) of the liver by the radioactivity of the ROI of the liver and the heart 15 min after injection. HH15 was calculated by dividing the radioactivity of the ROI of the heart 15 min after injection by the radioactivity of the ROI of the heart 3 min after injection[16,17].

SPECT analysis in ^{99m}Tc-GSA liver scintigraphy

Dynamic SPECT was performed using a dual-head gamma camera system equipped with low-energy, general-purpose collimators and a dedicated data processing unit (Millennium VG, GE, Tokyo, Japan). The in-plane spatial resolution of this system was 14 mm full width at half-maximum. After fasting overnight, the patient was placed in a supine position to ensure that the liver and lower part of the heart were within the detectors' field of view. ^{99m}Tc-GSA (185 MBq) was injected intravenously as a bolus. After it was confirmed that the entire liver was covered by the detector's view, dynamic SPECT data acquisition was started 1 min after injection and continued for 20 rotations in a 180° continuous rotation mode with an acquisition time of 1 min per rotation. In each rotation, the data from 60 projections were recorded in a 64 × 64 matrix (pixel size = 68.84 mm × 8.84 mm). SPECT images were reconstructed with a filtered back-projection method using a ramp filter after preprocessing with a Butterworth filter (cutoff frequency = 0.40 cycle per centimeter; order of 8) to obtain 8.84-mm-thick transaxial SPECT images. HC was determined from the SPECT data and was calculated with the outline extraction method using a program based on a radio pharmacokinetic model, as described by Shuke *et al*[14,15].

Conventional liver function tests

The serum albumin (Alb), total bilirubin (T-bil), and cholinesterase (Ch-E) levels; prothrombin time international normalized ratio (PT-INR); and platelet count (Plt) were measured in the peripheral blood before hepatectomy. The indocyanine green (ICG) test was conducted preoperatively, and the ICG clearance (ICG R15) was calculated using standard methods. The model for end-stage liver disease (MELD) score[18] and the Child-Turcotte-Pugh (CTP) score[19] were used as indices of liver dysfunctions.

Histopathological features of liver specimens

Liver fibrosis was diagnosed using surgical specimens, which were resected at a distance from the tumors. The degree of hepatic fibrosis was assessed and graded 0-6 according to the Ishak classification for chronic hepatitis[20]: 0: no fibrosis; 1: fibrous expansion of some portal areas, with or without short fibrous septa; 2: fibrous expansion of most portal areas, with or without short fibrous septa; 3: fibrous expansion of most portal areas with occasional portal-to-portal bridging; 4: fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central); 5: marked bridging (portal to portal and/or portal to central) with occasional nodules; and 6, cirrhosis, probable or definite. Scores of 0, 1, 2, and 3 were considered to reflect nonsevere fibrosis. Scores of 4, 5, and 6 were recorded as severe fibrosis. Tumor size, tumor number, and tumor vascular invasion (portal vein, hepatic artery, and hepatic vein) were evaluated using surgical specimens.

Table 1 Patient characteristics

Variables	*n* = 78
Age (yr)	66.7 ± 10.3
Gender (male/female)	63/15
HBs-Ag (+/-)	26/52
HCV-Ab (+/-)	21/57
Alcohol abuse (+/-)	10/68
NASH (+/-)	14/64
Diabetes mellitus (+/-)	25/73
Hyperlipidemia (+/-)	18/60
Platelets (× 10^4/mm^3)	16.6 ± 7.0
Prothrombin time (INR)	1.05 ± 0.11
Albumin (g/dL)	4.0 ± 0.6
Total bilirubin (mg/dL)	0.8 ± 0.3
Cholinesterase (U/L)	248 ± 70
Tumor size (cm)	49.6 ± 36.9
Tumor number	1.2 ± 0.5
Tumor vascular invasion (+/-)	21/57
Ishak classification 0/1/2/3/4/5/6	14/11/8/18/4/13/10
MELD score	5.3 ± 1.3
CTP score	5.2 ± 0.2
ICG R15 (%)	11.6 ± 6.0

HBs-Ag: Hepatitis B surface antigen; HCV-Ab: Hepatitis C virus antibody; NASH: Nonalcoholic steatohepatitis; MELD score: Model for end-stage liver disease score; CTP score: Child-Turcotte-Pugh score; ICG R15: Indocyanine green dye retention at 15 min.

Statistical analysis

The data are expressed as the mean ± SD unless otherwise stated. The data were analyzed using the Mann-Whitney *U* test, Pearson's correlation coefficient, and linear regression. These statistical analyses were performed using SPSS 11.0 for Windows (SPSS, Chicago, IL, United States). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) and interactive dot diagrams were created using MedCalc (software, 12.7.4; Ostend, Belgium).

RESULTS

Patient characteristics

The clinical characteristics of all participating patients are listed in Table 1. The mean age of the 78 patients was 66.7 ± 10.3 years, and there were 63 men. Of the 78 patients, 71 had chronic liver disease (chronic hepatitis B, n = 26; chronic hepatitis C, n = 21; non-alcoholic steatohepatitis, n = 14; and alcoholic hepatitis, n = 10). The remaining patients were diagnosed with normal livers. Concerning the degree of hepatic fibrosis, 10 patients were graded 6, 13 were graded 5, 4 were graded 4, 18 were graded 3, 8 were graded 2, 11 were graded 1, and 14 were graded 0. The mean ICG R15 was 11.6 ± 6.0.

Correlations between the degree of liver fibrosis and quantitative indices of liver functional reserve

Table 2 shows the correlations between the degree of liver fibrosis and preoperative liver function parameters. The degree of liver fibrosis was positively linearly correlated with ICG R15 and HH15 and negatively linearly correlated with HC.

Table 2 Correlations between the degree of liver fibrosis and quantitative indices for liver functional reserve

	r	*P* value
ICG R15	0.330	0.003
HH15	0.272	0.016
LHL15	-0.198	0.083
HC	-0.598	< 0.00001

The degree of liver fibrosis was correlated with ICG R15, HH15, and HC. ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

Correlations between quantitative indices for liver functional reserve and conventional liver function tests

As Table 3 shows, we evaluated the correlations between the preoperative parameters for liver function and conventional liver function tests. LHL15 was correlated with platelet count (r = 0.235, P = 0.038) and albumin level (r = 0.263, P = 0.020), and HH15 was correlated with total bilirubin level (r = 0.289, P = 0.010) and cholinesterase level (r = -0.263, P = 0.020). HC was correlated with all conventional liver function tests after liver resection: platelet count (r = 0.348, P = 0.002), prothrombin time (r = -0.287, P = 0.011), albumin level (r = 0.233, P = 0.040), total bilirubin level (r = -0.345, P = 0.002), and cholinesterase level (r = -0.419, P = 0.0001).

Univariate and multivariate stepwise regression analysis of various factors affecting liver fibrosis

Univariate analysis showed that platelet count (P < 0.001), prothrombin time (P = 0.032), total bilirubin level (P = 0.001), tumor size (P = 0.042), MELD score (P = 0.009), ICG R15 (P = 0.019), LHL15 (P = 0.042), HH15 (P = 0.0004), and HC (P < 0.0001) were significant predictors of severe cirrhosis. When we entered platelet count, prothrombin time, total bilirubin level, tumor size, MELD score, ICG R15, LHL15, HH15, and HC into a multivariate logistic regression model to identify variables with independent predictive value for severe fibrosis, we found that HC and LHL15 were the significant independent predictors (Table 4).

ROC curve and interactive dot diagrams of HC and LHL15 for the diagnosis of severe fibrosis

In Figure 1, we present the ROC curves for each of the 2 variables, HC and LHL15, that were identified as the significant independent predictors of severe fibrosis. The AUC of the ROC curves for HC and LHL15 were 0.826 and 0.641, respectively. There was a significant difference between the two values (P = 0.0146). Based on the analysis employing interactive dot diagrams, the cutoff values for predicting severe cirrhosis with the highest sensitivity and specificity were 298 (sensitivity, 77.8%; specificity, 84.3%) for HC and 0.926 (sensitivity, 74.1%; specificity, 60.8%) for LHL15.