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Original Article

Benefit of technetium-99*m* galactosyl human serum albumin scintigraphy instead of indocyanine green test in patients scheduled for hepatectomy

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Aim: The aim of this study was to evaluate the benefit of technetium-99*m* galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy instead of the indocyanine green retention rate at 15 min (ICGR15) in the patients scheduled for hepatectomy, paying special attention to the factors causing the discrepancy between the ICGR15 and the hepatic uptake ratio of ^{99m}Tc-GSA scintigraphy at 15 min (LHL15).

Methods: The medical records on the 197 patients who underwent hepatectomy between 2006 and 2010 were retrospectively reviewed. We defined ICG-good as less than 15% at ICGR15 and ICG-poor as 15% or more, and LHL-good as 0.9 or more at LHL15 and LHL-poor as less than 0.9.

Results: The patients were divided into the four groups ICG-good/LHL-good, ICG-good/LHL-poor, ICG-poor/LHL-good and ICG-poor/LHL-poor, showing the discrepancy between the two tests in 47 (23.8%) patients. In the ICG-good group, the incidence of liver cirrhosis (LC) was significant higher in the ICG-good/LHL-poor group than in the ICG-good/LHL-good group at 54.5% versus 14.9% (P = 0.014). In the ICG-poor group, the incidence of LC was significant lower in the ICG-poor/LHL-good group than in the ICG-poor/LHL-poor group at 44.4% versus 77.8% (P = 0.004). In multivariate analysis of the factors causing discrepancy, the factor contributing to LHL-poor was hepatitis C infection and those contributing to LHL-good were albumin and hyaluronic acid.

Conclusion: ^{99m}Tc-GSA scintigraphy is very helpful to assess the hepatic functional reserve in the ICG-good patients who have hepatitis C infection and in the ICG-poor patients who have relatively good levels of albumin and hyaluronic acid.

Key words: hepatic functional reserve, ICGR15, LHL15, liver failure

INTRODUCTION

IN ASIAN COUNTRIES, patients suffering from primary hepatocellular carcinoma (HCC) are the main candidates for hepatic resection and most of them are associated with liver cirrhosis (LC) and chronic hepatitis (CH), which limits hepatic resection. Postoperative liver failure, a major cause of early death, occurs exclusively after excessive resection, when adequate hepatic functional reserve is not considered.

Various liver function tests were used to evaluate the hepatic functional reserve and the indocyanine green retention rate at 15 min (ICGR15) has been widely used.[1] In Japan, the Makuuchi criteria have been widely used to decide the extent of hepatic resection.[2] However, the discrepancy between ICGR15 and histological findings of the liver are occasionally observed in patients with jaundice and intrahepatic shunt, and ICGR15 does not always represent accurate hepatic functional reserve.

The technetium-99*m* galactosyl human serum albumin (^{99m}Tc-GSA) is a liver scintigraphy agent which specifically binds to the asialoglycoprotein receptors on the hepatocellular membrane. Chronic liver diseases have been known to cause a significant decrease in asialoglycoprotein receptors in the liver together with accumulation of plasma asialoglycoproteins.[3,4] The hepatic uptake ratio of ^{99m}Tc-GSA scintigraphy at 15 min (LHL15) is correlated with other useful parameter of liver function[5–7] and thus some special institutions utilize it as preoperative determination of the surgical procedure for hepatectomy. However, some of the

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patients demonstrate discrepancy between ICGR15 and LHL15, and the histological severity of disease is better reflected by ^{99m}Tc-GSA scintigraphy.[6,8]

There are two patterns in the discrepancy between ICGR15 and LHL15: the patients with poor ICGR15 level/good LHL15 level and those with good ICGR15 level/poor LHL15 level. The former pattern is thought to be observed in the patients who have an intra- or extrahepatic shunt resulting in the changes of hepatic blood flow or the patients with jaundice.[8] However, the causes of the latter pattern are not well known. The aim of this study was to evaluate which patients have benefit from ^{99m}Tc-GSA scintigraphy, paying special attention to the factors causing the discrepancy between ICGR15 and ^{99m}Tc-GSA scintigraphy.

METHODS

WE RETROSPECTIVELY REVIEWED the electronic medical records of the 197 consecutive patients who underwent hepatectomy at our institution between January 2006 and December 2010, excluding three patients with ICG intolerance (Table 1). Intrahepatic cholangiocarcinoma was defined as peripheral type alone without bilioenteric anastomosis. Hilar type with bilioenteric anastomosis was defined as perihilar cholangiocarcinoma, which includes hilar bile duct carcinoma according to the previous report.[9] All patients with obstructive jaundice (OJ) were treated preoperatively by endoscopic retrograde biliary drainage or percutaneous transhepatic biliary drainage and their serum total bilirubin decreased to less than 2 mg/dL before surgery.

Indocyanine green retention rate at 15 min and LHL15 were examined in all of the 197 patients within 1 month before hepatectomy. According to our previous study,[10] postoperative morbidity and mortality rates were very high in the patients who had LHL15 of less than 0.9 and/or ICGR15 of 15% or more. Therefore, we determined the cut-off values of ICGR15 as 15% and LHL15 as 0.90, and defined ICG-good as less than 15% at ICGR15 and ICG-poor as 15% or more, and LHL-good as 0.9 or more at LHL15 and LHL-poor as less than 0.9. Consequently, the 197 patients were divided into the four groups: ICG-good/LHL-good, ICG-good/LHL-poor, ICG-poor/LHL-good and ICG-poor/LHL-poor. We defined the discrepancy between ICGR15 and LHL15 as ICG-good/LHL-poor and ICG-poor/LHL-good.

The results of standard liver function tests (albumin, total bilirubin [T-Bil], platelet count, prothrombin time international normalized ratio [PT-INR], activated partial thromboplastin time [APTT], hyaluronic acid [HA]) were collected from the medical records of each patient.

The type of hepatectomy was determined by the following factors: ICGR15, LHL15, and future remnant liver volume using computed tomography (CT) volumetry. The whole liver volume, excluding the liver tumor and the future remnant liver volume, was obtained by adding the volumes of the individual slices.[11] Our institutional criterion for safe hepatectomy in normal liver (LHL15, >0.9) is that more than 40% of the total liver volume should be preserved. In the patients with no discrepancy between ICGR15 and LHL15, it was determined according to the Makuuchi criteria. In the patients with discrepancy, one sectionectomy or limited hepatectomy was indicated in ICG-good/LHL-poor patients and two sectionectomies were indicated in ICG-poor/LHL15-good patients. Portal vein embolization (PVE) was indicated when the future remnant liver volume was estimated as less than 40%. Actually, 22 patients underwent PVE preoperatively.

Table 1 Patient characteristic

Average age	67.1 (38–86)
Sex ration (M : F)	144:53
Disease	
Hepatocellular carcinoma	123
Intrahepatic cholangiocarcinoma	12
Perihilar cholangiocarcinoma	25
Gallbladder carcinoma	5
Metastatic tumor	15
Hemangioma	5
Intraductal papillary neoplasm of the bile duct	3
Intrahepatic stone	2
Other diseases	7
Background liver diseases (NL : OJ : CH : LC)	52:20:58:67
Hepatectomy	
Limited resection (segmentectomy, partial resection)	76
Sectionectomy	36
2 or 3 sectionectomies	85
Surgical outcome	
Blood loss median (25th percentile, 75th percentile, mL)	1368 (542–2700)
Operation time, median (25th percentile, 75th percentile, min)	389 (277–483)

CH, chronic hepatitis; LC, liver cirrhosis; NL, normal liver; OJ, obstructive jaundice.

Postoperative hyperbilirubinemia was defined as T-Bil greater than 4 mg/dL according to Kawamura *et al.*[12] Signs of postoperative liver failure were defined as prolonged ascites (>4 weeks) and postoperative T-Bil greater than 10 mg/dL. All-cause death in 30 days was defined as any death within 30 days of operation, whenever it occurred. All-cause death in the hospital was defined as death that occurred during the same hospital stay, irrespective of the length of hospital stay.

Statistical analyses

Correlations were evaluated with Pearson's correlation coefficients. Categorical variables were assessed using the χ^2-test or Fisher's exact test, and continuous variables were assessed using Student's *t*-test or Mann–Whitney *U*-test. A logistic stepwise regression model was used to identify predictive factors for discrepancy between ICGR15 and LHL15. $P < 0.05$ was considered statistically significant. All analyses were performed with the SPSS package (version 19; SPSS, Chicago, IL, USA).

RESULTS

Surgical results after hepatectomy based on preoperative ICGR15

IN THE TOTAL of cases, median operative time was 389 min (25th–75th percentile, 277–483), and median blood loss was 1368 mL (25th–75th percentile, 542–2700) as shown in Table 1. Table 2 shows operative procedures, background liver diseases, sign of postoperative liver failure, and all-cause death both within 30 days and in the hospital according to ICGR15 stratification of the Makuuchi criteria. Among the 70 patients with ICGR15 of less than 10% which indicates that right hepatectomy can be tolerated, 40 (57.1%) underwent two or three sectionectomies, while 18 (25.7%) had limited hepatectomy. Among the 26 patients with ICGR15 within the range of 20–29% which indicates that segmentectomy should be selected, 15 (57.7%) underwent limited hepatectomy, while nine (34.6%) underwent two or three sectionectomies. Thus, in 25–35% of the patients, we selected hepatectomy procedure unmatched with the Makuuchi criteria. All-cause death in 30 days occurred in four patients (2.0%), whose cause of death was liver failure, portal vein injury, sepsis and asphyxia in one each. All-cause death in the hospital occurred in 18 patients (9.1%). Excluding all-cause deaths within 30 days, 14 deaths occurred from 35 to 149 days after hepatectomy: pneumonia in four, portal vein thrombosis in three, recurrent tumor in two, sepsis in two, liver failure in two, and portal vein injury in one. In the present study, the all-cause death rates at 30 days and in the hospital were 2.0% and 9.1%, respectively, which were significantly higher than those of recent reports.[13,14] When the all-cause death rates were further examined according to the factors such as previous hepatectomy, radiofrequency ablation (RFA) and bilioenteric anastomosis, those at 30 days and in the hospital were much higher in the 27 HCC patients with previous hepatectomy and/or RFA than in the 96 HCC patients without them, at 3.7% and 14.8% versus 0% and 4.2% ($P = 0.058$ and $P = 0.047$), respectively. In the 29 patients with biliary malignancy who received bilioenteric anastomosis, those were 3.4% and 27.6%, respectively.

Correlation between LHL15 and ICGR15, and the other parameters

Fig. 1 shows correlation between LHL15, ICGR15 and the other liver function parameters. There was mild cor-

Table 2 Surgical results after hepatectomy based on preoperative ICGR15

	<10 ($n = 70$)	10–19 ($n = 87$)	20–29 ($n = 26$)	≥30 ($n = 14$)
Operation (2 or 3 Sec : l Sec : limited)	40:12:18	34:20:33	9:2:15	2:2:10
Background liver diseases (NL : OJ : CH : LC)	29:7:23:11	20:12:27:28	3:0:6:17	0:1:2:11
Signs of postoperative liver failure	5 (7.1%)	13 (14.9%)	2 (7.7%)	1 (7.1%)
Background liver diseases (NL : OJ : CH : LC)	1:1:2:1	4:5:0:4	0:0:0:2	0:0:0:1
Operation (2 or 3 Sec : l Sec : limited)	5:0:0	9:4:0	1:0:1	0:0:1
All-cause death in the hospital	4 (5.7%)	12 (13.8%)	1 (3.8%)	1 (7.1%)
All-cause death within 30 days	1 (1.4%)	3 (3.4%)	0	0
Background liver diseases (NL : OJ : CH : LC)	0:2:2:0	4:3:1:4	1:0:0:0	0:0:0:1
Operation (2 or 3 Sec : l Sec : limited)	4:0:0	9:2:1	1:0:0	0:0:1

CH, chronic hepatitis; LC, liver cirrhosis; NL, normal liver; OJ, obstructive jaundice; Sec, sectionectomy.

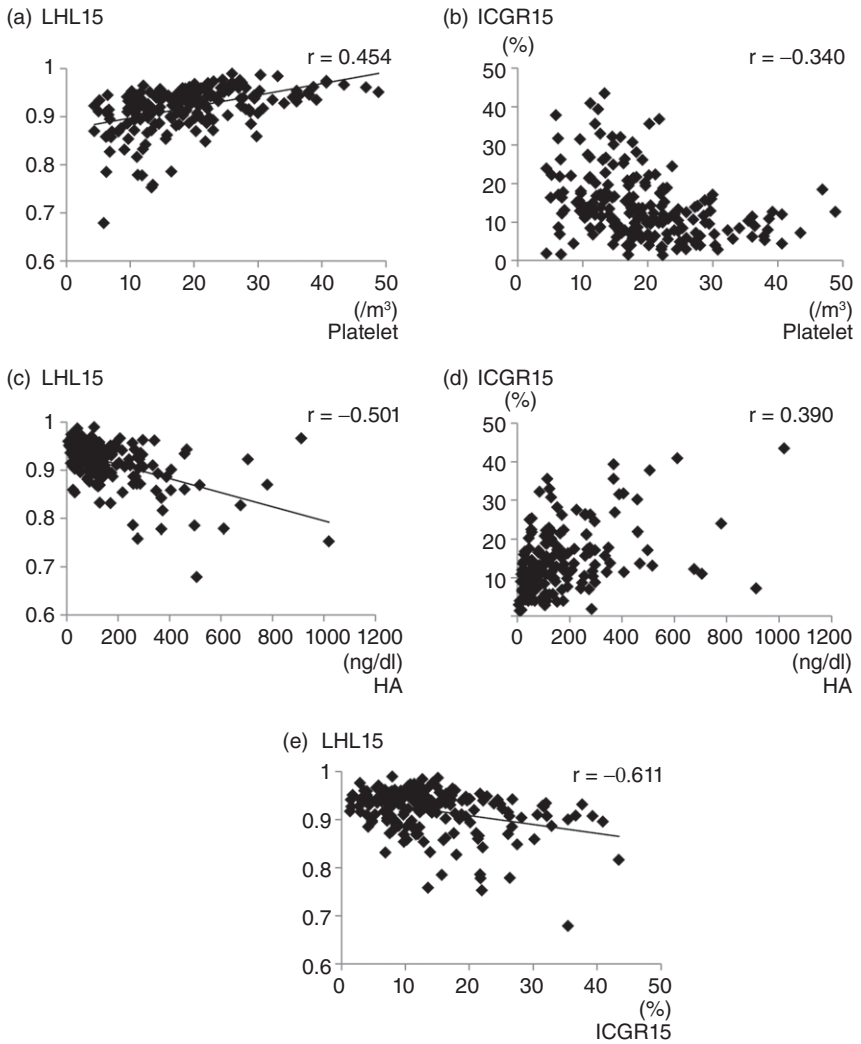

Figure 1 Correlation between hepatic uptake ratio of the technetium-99*m* galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy at 15 min (LHL15), indocyanine green retention rate at 15 min (ICGR15) and other parameters. (a) Correlation between platelet count and LHL15 ($r = 0.454$, $P < 0.001$). (b) Correlation between platelet and ICGR15 ($r = –0340$, $P < 0.001$). (c) Correlation between hyaluronic acid (HA) and LHL15 ($r = –0.501$, $P < 0.001$). (d) Correlation between HA and ICGR15 ($r = 0.390$, $P < 0.001$). (e) Correlation between ICGR15 and LHL15 ($r = –0.611$, $P < 0.001$).

relation between LHL15 and platelets ($r = 0.454$), but no correlation between ICGR15 and platelets. Additionally, there was significant correlation between LHL15 and HA ($r = –0.501$), but no correlation between ICGR15 and HA. Finally, LHL15 and ICGR15 showed significant correlation ($r = –0.611$). However, LHL15 and ICGR15 were not correlated with the other parameters such as albumin, T-Bil, PT-INR and APTT.

Grouping according to ICGR15 and LHL15

According to our definition based on ICGR15 and LHL15, patients were divided into the four groups: ICG-good/LHL-good ($n = 114$), ICG-good/LHL-poor ($n = 11$), ICG-poor/LHL-good ($n = 36$) and ICG-poor/LHL-poor ($n = 36$) (Fig. 2). Therefore, the discrepancy between ICGR15 and LHL15 were found in 47 (23.8%) patients: ICG-good/LHL-poor ($n = 11$) and ICG-poor/LHL-good ($n = 36$). On the following, we examined clinical characteristics of the two discrepancy groups by comparing ICG-good/LHL-poor versus ICG-good/LHL-good and ICG-poor/LHL-good versus ICG-poor/LHL-poor.

Comparison between ICG-good/LHL-poor and ICG-good/LHL-good

In background liver diseases, the incidence of LC was significantly higher in the ICG-good/LHL-poor group than in the ICG-good/LHL-good group, at 54.5% versus 14.9% ($P = 0.001$). In operative procedure, the incidence of two or three sectionectomies were significant lower in the ICG-good/LHL-poor group than the ICG-good/LHL-good group, at 9.1% versus 55.3%

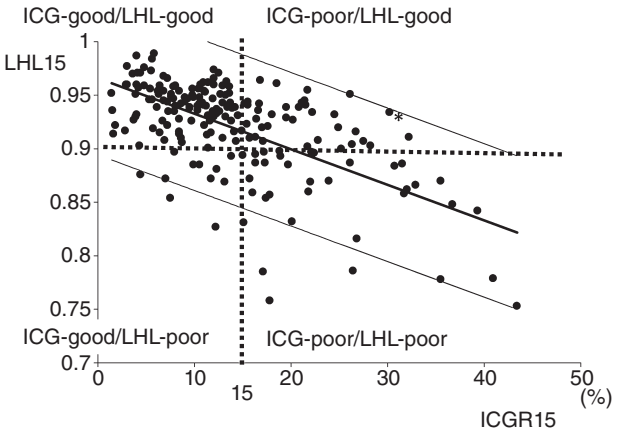

Figure 2 Grouping according to indocyanine green retention rate at 15 min (ICGR15) and hepatic uptake ratio of the technetium-99*m* galactosyl human serum albumin scintigraphy at 15 min (LHL15). According to our definition based on ICGR15 and LHL15, patients were divided into the four groups: ICG-good/LHL-good ($n = 114$), ICG-good/LHL-poor ($n = 11$), ICG-poor/LHL-good ($n = 36$) and ICG-poor/LHL-poor ($n = 36$). The thick solid line represents the regression of the correlation. The thin solid line represents the 95% confidence range of the correlation.

($P = 0.009$). No significant differences were found between the two groups in the occurrence of postoperative hyperbilirubinemia, liver failure and in-hospital death (9.1% vs 25.4%, 9.1% vs 11.4% and 18.2% vs 11.4%, respectively) (Fig. 3). In univariate analysis between the ICG-good/LHL-poor group ($n = 11$) and the ICG-good/LHL-good group ($n = 114$), the factors contributing to LHL-poor were HA, platelet counts and hepatitis C infection. Multivariate analysis revealed that hepatitis C infection was an independent risk factor ($P = 0.001$) (Table 3).

Comparison between ICG-poor/LHL-good and ICG-poor/LHL-poor

In background liver diseases, the incidence of LC was significant lower in the ICG-poor/LHL-good group than in the ICG-poor/LHL-poor group, at 44.4% versus 77.8% ($P = 0.004$). No significant differences were observed between the two groups in operative procedure (incidence of two or three sectionectomies), postoperative hyperbilirubinemia, liver failure and in-hospital death (36.1% vs 22.2%, 11.1% vs 13.9%, 8.3% vs 11.1%, 5.6% vs 5.6%, respectively) (Fig. 4). In univariate analysis between the ICG-poor/LHL-good group ($n = 36$) and ICG-the poor/LHL-poor group ($n = 36$), the factors contributing to LHL-good were albumin and HA. Multivariate analysis revealed that albumin and HA were independent risk factors ($P = 0.021$ and 0.019, respectively) (Table 4).

Pathological findings of typical cases with discrepancy between ICGR15 and LHL15

In Fig. 5(a), a typical discrepancy case of ICG-good/LHL-poor is shown. A 65-year-old woman with HCC and hepatitis C infection had normal liver function except for an LHL15 of 0.876. Because a tumor measuring 1.6 cm was located near the liver surface in S7, we performed laparoscopic partial liver resection. The operative time and blood loss were 163 min and 10 mL, respectively. The peak values of aspartate aminotransferase and alanine aminotransferase reached 386 and 363 IU/L, respectively, on postoperative day 3, and the patient was discharged without postoperative complications on postoperative day 12. The pathological finding of the resected specimen showed liver cirrhosis.

In Fig. 5(b), a typical discrepancy case of ICG-poor/LHL-good is shown. A 76-year-old man, who underwent sigmoidectomy for sigmoid colon cancer 1 year prior, developed a single hepatic metastatic tumor of 3.8 cm in S7 and another tumor of 1 cm located in the ileocecal region. Liver function tests were normal except for ICGR15 of 26.1%. We performed partial liver resection of S7 and ileocecal resection: the operative time and blood loss were 472 min and 2880 mL, respectively. The patient was discharged without postoperative complications on postoperative day 12. The pathological finding of the resected specimen showed normal liver.

DISCUSSION

ALTHOUGH THE MAKUUCHI criteria using ICGR15 are not complex and used widely in Japan and Asia countries to determine the safe limit of hepatectomy, our present study revealed that hepatectomy procedures unmatched with that criteria were performed in approximately 30% of the patients. Interestingly, the incidences of postoperative liver failure and all-cause death both within 30 days and in the hospital did not show a statistically significant difference among the four ICGR15 stratification groups. This may be because we evaluated hepatic functional reserve by using not only ICGR15 but also LHL15. However, it was a big problem which parameter we should use to make a final decision of hepatectomy procedure, especially when the two parameters showed discrepancy. In such instances, we had determined operative procedure

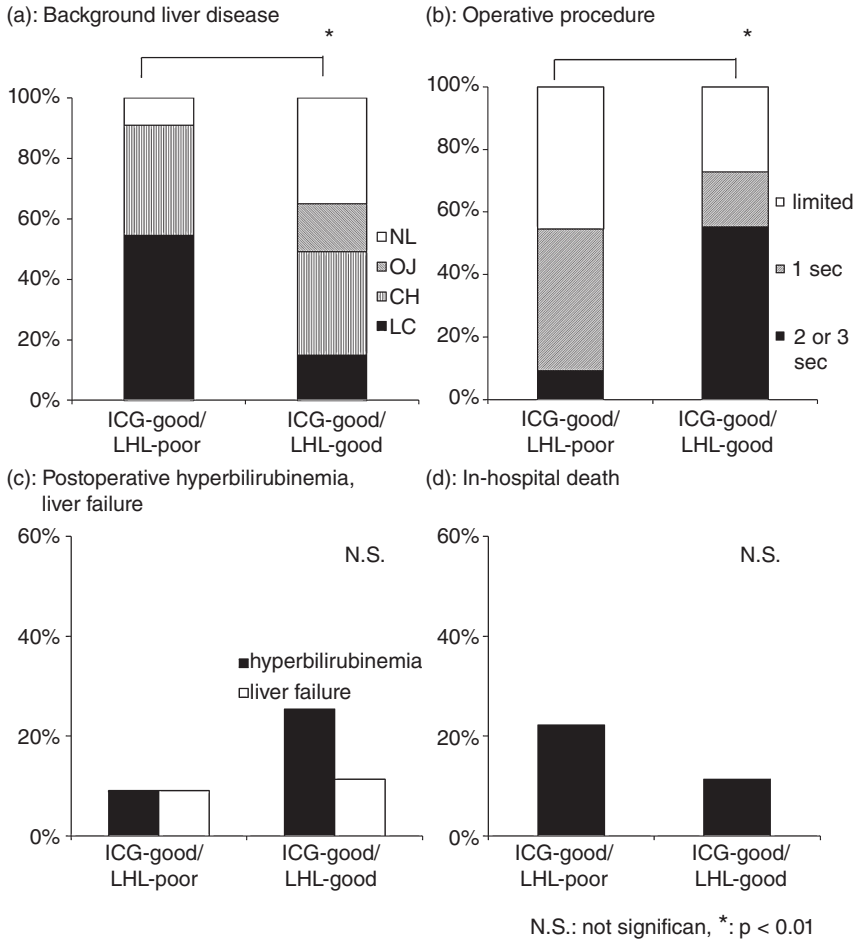

Figure 3 Background liver diseases, operative procedure, postoperative liver failure and in-hospital death in ICG-good group. (a) Background liver diseases (the incidence of liver cirrhosis, $P = 0.001$). (b) Operative procedure (the incidence of two or three sectionectomies, $P = 0.009$). (c) Incidence of postoperative hyperbilirubinemia, liver failure. (d) In-hospital death.

Table 3 Univariate and multivariate analysis between the ICG-good/LHL-poor group and ICG good/LHL-good group

	ICG-good/LHL-poor ($n = 11$)	ICG-good/LHL-good ($n = 114$)	*P*-value, univariate analysis	*P*-value, stepwise logistic regression
Age (median ± SD, years)	71.1 ± 9.9	65.6 ± 9.9	0.076	0.664
Sex (male / female)	9/2	80/34	0.641	0.387
Albumin (median ± SD, g/dL)	3.8 ± 0.6	3.8 ± 0.5	0.096	0.339
T-Bil median (25th percentile, 75th percentile, mg/dL)	0.6 (0.5–0.65)	0.6 (0.4–0.8)	0.974	0.824
Platelet count (median ± SD, /m^3)	14.5 ± 6.8	22.1 ± 8.7	0.006	0.114
PT-INR (median ± SD)	1.1 ± 0.1	1.0 ± 0.2	0.493	0.756
APTT (median ± SD, s)	33.0 ± 6.5	31.1 ± 4.7	0.334	0.888
HA median (25th percentile, 75th percentile, ng/dL)	141 (85–321)	67 (36–140)	<0.001	0.082
Virus infection				
HBV (positive/negative)	0/11	17/94	0.346	0.612
HCV (positive/negative)	10/1	25/89	<0.001	0.001
Obstructive jaundice (positive/negative)	0/11	13/101	0.505	0.670

Underlined data indicates statistical significance. APTT, activated partial thromboplastin time; HA, hyaluronic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; PT-INR, prothrombin time international normalized ratio; SD, standard deviation; T-Bil, total bilirubin.

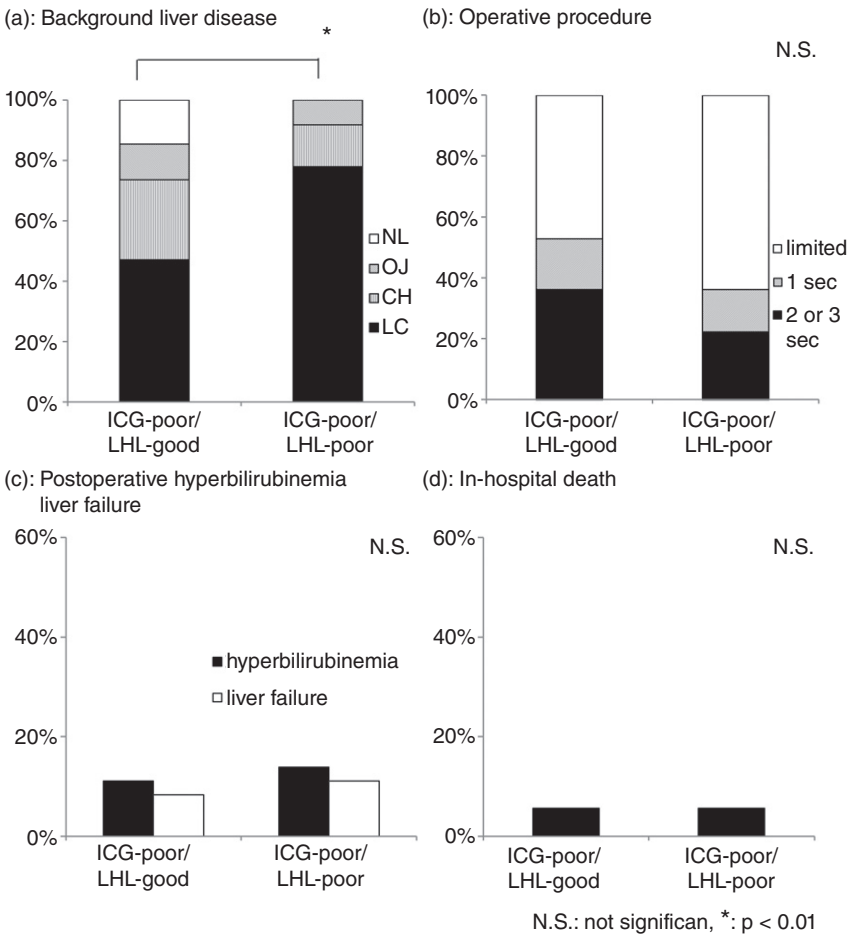

Figure 4 Background liver diseases, operative procedure, postoperative liver failure and in-hospital death in the ICG-poor group. (a) Background liver diseases (the incidence of liver cirrhosis, $P = 0.004$). (b) Operative procedure (the incidence of two or three sectionectomies). (c) Incidence of postoperative hyperbilirubinemia, liver failure. (d) In-hospital death.

Table 4 Univariate and multivariate analysis between ICG-poor/LHL-good group and ICG-poor/LHL-poor group

	ICG-poor/LHL-good ($n = 36$)	ICG-poor/LHL-poor ($n = 36$)	*P*-value, univariate analysis	*P*-value, stepwise logistic regression
Age (median ± SD, years)	70.1 ± 8.1	67.5 ± 8.4	0.197	0.511
Sex (male/female)	30/6	25/11	0.165	0.266
Albumin (median ± SD, g/dL)	3.7 ± 0.5	3.3 ± 0.5	0.006	0.021
T-Bil median (25th percentile, 75th percentile, mg/dL)	0.7 (0.6–1.2)	0.8 (0.5–1.15)	0.820	0.344
Platelet count (median ± SD, /m^3)	16.9 ± 7.9	13.7 ± 6.0	0.053	0.099
PT-INR (median ± SD)	1.1 ± 0.1	1.1 ± 0.1	0.099	0.837
APTT (median ± SD, s)	31.5 ± 5.2	32.7 ± 4.3	0.324	0.880
HA median (25th percentile, 75th percentile, ng/dL)	137 (82.5–210.5)	238.5 (129–372.7)	0.002	0.019
Virus infection				
HBV (positive/negative)	5/31	3/33	0.453	0.533
HCV (positive/negative)	13/23	19/17	0.155	0.533
Obstructive jaundice (positive/negative)	3/33	2/34	0.691	0.723

Underlined data indicates statistical significance. APTT, activated partial thromboplastin time; HA, hyaluronic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; PT-INR, prothrombin time international normalized ratio; SD, standard deviation; T-Bil, total bilirubin.

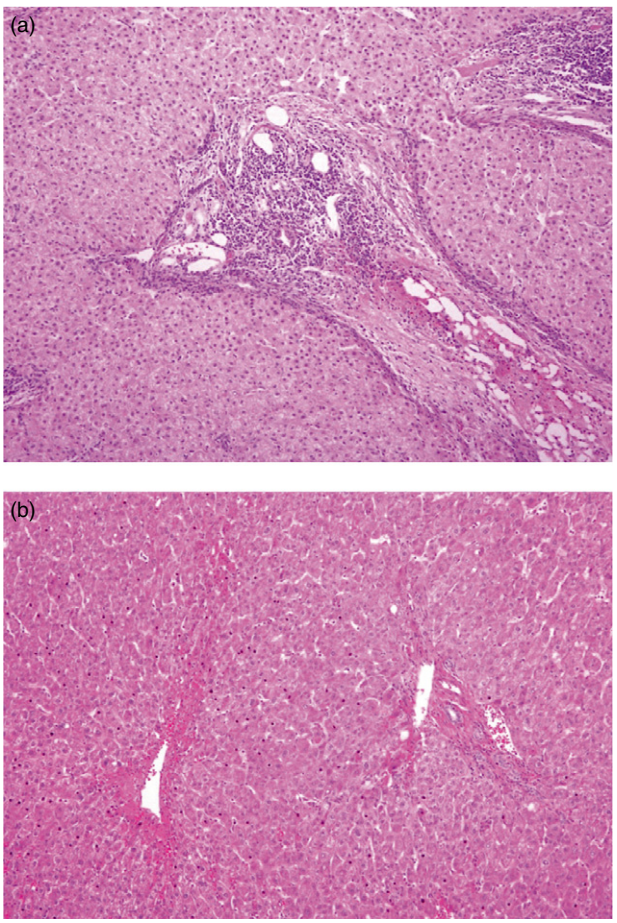

Figure 5 Pathological findings of typical cases with discrepancy between indocyanine green retention rate at 15 min (ICGR15) and hepatic uptake ratio of the technetium-99*m* galactosyl human serum albumin scintigraphy at 15 min (LHL15). (a) Typical discrepancy case of ICG-good/LHL-poor: a 65-year-old hepatocellular carcinoma (HCC) woman with hepatitis C infection. Her laboratory data showed normal liver function except for LHL15 of 0.876 (ICGR15, 4.4%; albumin, 4.5 g/dL, total bilirubin; 0.5 mg/dL, prothrombin time international normalized ratio, 1.00; hyaluronic acid, 90 ng/dL). The pathological finding of the resected specimen showed liver cirrhosis. (b) Typical discrepancy case of ICG-poor/LHL-good: a 76-year-old man with metastatic tumor. His laboratory data showed normal liver function except for ICGR15 of 26.1% (LHL15, 0.951; albumin, 3.6 g/dL; total bilirubin, 0.5 mg/dL; prothrombin time international normalized ratio, 0.99; hyaluronic acid, 171 ng/dL). The pathological finding of the resected specimen showed normal liver.

according to LHL15 levels as shown in the following data: among 87 patients with ICGR15 within the range of 10–19%, no patients in the ICG-good/LHL-poor group ($n = 6$) underwent right hepatectomy, while four patients in the ICG-poor/LHL-good group ($n = 17$) underwent right hepatectomy.

The ICGR15 level is mainly dependent on hepatic blood flow and the intra- and extrahepatic shunt,[15] and moreover it has been shown to be an unreliable marker for hepatic functional reserve in jaundiced patients because the ICG receptor of hepatocytes also has an affinity for bilirubin.[16] Therefore, the ICGR15 level does not always reflect hepatic functional reserve.

The LHL15 has been identified as a more reliable test for assessing hepatic functional reserve, because the histological activity index (HAI), which means severity of chronic liver damage, correlates significantly with LHL15 but not with ICGR15, and the significance of the correlation between LHL15 and other parameters appears to be much better as compared to ICGR15.[6,8,17] Kudo *et al.*[5] reported that LHL15 strongly reflected the hepatocellular function in the patients with portocaval shunt, even when they had a decreased hepatic flow. Moreover, unlike ICG, ^{99m}Tc-GSA uptake of the liver is not directly inhibited by hyperbilirubinemia and can be used to evaluate liver function during cholestasis because the asialoglycoprotein receptor does not bind to bilirubin. However, when period of jaundice is prolonged, ^{99m}Tc-GSA uptake decreases, probably because affinity of the asialoglycoprotein receptor is impaired by damaged hepatocytes due to prolonged jaundice.[18] Furthermore, Kokudo *et al.*[19] reported the clinical usefulness of hepatic asialoglycoprotein receptor analysis in liver surgery by conducting univariate and multivariate analysis for the detection of cirrhotic patients and prediction of morbidity after hepatic resection. They examined ICGR15, LHL15, total hepatic asialoglycoprotein receptor amount and hepatic parenchymal volume among patients with normal, cirrhotic and non-cirrhotic damaged liver. As a result, total receptor amount was a significant indicator of LC and receptor amount of the remnant liver was a significant parameter for the prediction of liver failure.

In our present study, LHL15 was significantly correlated with HA and platelet count, but ICGR15 was not significantly correlated with any other liver function test except for LHL15. Previous reports also revealed significant correlation between LHL15 and HA,[8,17] though the precise mechanism is still unclear. Because HA is liberated into the blood mainly from connective tissue cells and is cleared exclusively by hepatic sinusoidal endothelial cells (SEC), serum HA levels have been found to reflect SEC function. SEC play an important role in maintaining liver function by facilitating continuous exchange of various important factors between blood

and hepatocytes and by scavenging blood-borne compounds such as denatured proteins and HA, and thus impaired SEC damage hepatocytes. Recently, Yachida *et al.*[20] reported that in patients undergoing hepatectomy, serum HA is a simple clinical marker for portal venous pressure and a reliable auxiliary parameter of hepatic functional reserve in combination with other liver function tests. As for the correlation between LHL15 and platelet count, it is considered that low preoperative platelet count is related to portal hypertension, hypersplenism and hepatic fibrosis which are associated with increased serum HA.[21–23] Additionally, the previous study examining the relationship between ICGR15 and LHL15 in patients scheduled for hepatectomy revealed that portal pressure correlated significantly with LHL15 but not with ICGR15.[8] Therefore, LHL15 may reflect non-hepatocyte cells such as SEC function and portal pressure.

Similar to our present study, the previous three studies promoted awareness of the discrepancy between ICGR15 and LHL15, revealing that LHL15 reflects hepatic functional reserve more accurately than ICGR15.[6,8,12] Nanashima *et al.*[8] reported that the discrepancy was found in 8% of the patients when it was defined as out of 95% of the reliable range of correlation. In the patients showing the discrepancy, ICG-good/LHL-poor patients (according to our classification) had higher histological severity of chronic hepatitis or cirrhosis and ICG-poor/LHL-good patients had obstructive jaundice or intrahepatic shunt. Although a previous two reports defined the discrepancy as out of 95% of the reliable range of correlation, this definition is clinically inappropriate.[6,8] As shown in Figure 2, for example, the patient with ICGR15 of 30.2% and LHL15 of 0.934, who had intrahepatic cholangiocarcinoma with obstructive jaundice, is not defined as discrepancy according to the previous definition. This patient, however, should be defined as a discrepancy from the clinical point of view, because major hepatectomy is contraindicated according to ICGR15 level defined by the Makuuchi criteria and not contraindicated according to LHL15 level defined by our previous study.[10] Therefore, our definition of the discrepancy between ICGR15 and LHL15 is more appropriate.

Kawamura *et al.*[12] calculated the conversion formula for ICGR15 based on the GSA test (converted ICGR15), and examined the clinical outcome in the patients with discrepancy between ICGR15 and converted ICGR15. This resulted in a significantly high frequency of postoperative hyperbilirubinemia. The definition of discrepancy in the Kawamura study was similar to the results of our study; however, when we applied our data to Kawamura's model, no relationship was observed between the discrepancy cases in their conversion models and postoperative hyperbilirubinemia. This may be because the number in our study was small and our selection of hepatectomy was considered to be properly made by using ICGR15 and LHL15.

Concerning compatibility between ICGR15 of 15% and LHL15 of 0.9, our present data showed that it was relevant according to the following analysis (Fig. 2). In the 125 patients with ICGR15 of less than 15%, 114 (91.2%) had LHL15 of 0.9 or more, while in the 72 patients with ICGR15 of 15% or more, 36 (50%) had LHL15 of less than 0.9. On the other hand, in the 70 patients with ICGR15 of less than 10%, 65 (92.9%) had LHL15 of 0.9 or more, while in the 127 patients with ICGR15 of 10% or more, only 42 (33.1%) had LHL15 of 0.9 or more. Finally, in the 157 patients with ICGR15 of less than 20%, 131 (83.4%) had LHL15 of 0.9 or more, while in the 40 patients with ICGR15 of 20% or more, 21 (52.5%) had LHL15 of 0.9 or more. With regard to sensitivity and specificity, the cut-off values of ICGR15 as 15% and LHL15 as 0.90 were considered relevant. Furthermore, the patient with ICGR15 of less than 15% was comparable to LHL15 of 0.90 or more.

In the present study, multivariate analysis on the factors causing discrepancy between ICGR15 and LHL15 revealed that the factor contributing to ICG-good/LHL-poor was hepatitis C infection. Furthermore, the incidence of LC was significantly higher in the ICG-good/LHL-poor group than in the ICG-good/LHL-good group. Kamohara *et al.*[24] also performed the combination analysis between ICGR15 levels and LHL15 of less than 0.9 (LHL-poor) or 0.9 or more (LHL-good), paying attention to HAI of liver. In the patients with ICGR15 of 15–20%, HAI score was significantly higher in the LHL-poor group than in the LHL-good group, while in the patients with ICGR15 of more than 25% HAI score did not differ between the LHL-poor and LHL-good groups. These data indicate that LHL15 can reflect histological liver damage such as fibrosis more sensitively, compared to ICGR15. Furthermore, Kira *et al.*[25] examined the relationship between LHL15 levels and four indices of HAI in the patients with chronic active hepatitis type C, and they revealed that decreased LHL15 levels were significantly correlated with hepatic fibrosis. According to the previous studies, histological features such as necrosis, inflammation and fibrosis differ between hepatitis B and C. In hepatitis C, micronodular cirrhosis, lymphoid aggregates, steatosis and bile duct damage are significantly more common compared to hepatitis B.[26–28]

Taking these findings together, we hypothesize that hepatitis C infection causes hepatic fibrosis and necrosis during the early stage of hepatitis, which may be detected more accurately by LHL15 than by ICGR15. On the other hand, the incidence of LC was significantly lower in the ICG-poor/LHL-good group than in the ICG-poor/LHL-poor group. Several reports indicated that the factors contributing to ICG-poor/LHL-good were OJ and the intra- and extrahepatic shunt.[6,8,29] However, our study showed that those were not OJ but albumin and HA. Because albumin and HA reflect hepatocyte and non-hepatocyte (SEC) functions, respectively, which may be detected more accurately by LHL15 level as compared to ICGR15 level, we hypothesize that hepatocyte as well as non-hepatocyte functions are more preserved in the ICG-poor/LHL-good group than in the ICG-poor/LHL-poor group.

In the present study, we revealed that all-cause death in the hospital was very high in patients who had undergone hepatectomy requiring bilioenteric anastomosis. According to the multicenter clinical registry data in the USA, postoperative mortality in the patients with cholangiocarcinoma was significantly higher in cases of hepatectomy with bilioenteric anastomosis than in hepatectomy alone.[30] According to a recent report from a high volume center in Japan, in-hospital mortality after hepatectomy with bilioenteric anastomosis for biliary carcinoma was very high (15% from 1991 to 2000), while the rate decreased significantly to 2.6% during 2001 to 2008.[31] Because the in-hospital mortality rate in our institution is very high for patients who receive hepatectomy with bilioenteric anastomosis, our surgical techniques and protocols require further improvements and refinements for perioperative management.

Technetium-99*m* galactosyl human serum albumin scintigraphy is therefore considered a more reliable diagnostic approach for evaluating hepatic functional reserve. Because the present study revealed that the discrepancy between ICGR15 and LHL15 was found in approximately 20% of patients, ^{99m}Tc-GSA scintigraphy and the ICG test should be performed in every patient scheduled for hepatectomy as much as possible, especially in the ICG-good patients who have hepatitis C infection and in the ICG-poor patients who have relatively good levels of albumin and HA.

REFERENCES

1 Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. *J Clin Invest* 1960; **39:** 592–600.

2 Makuuchi M, Kosuge T, Takayama T *et al*. Surgery for small liver cancers. *Semin Surg Oncol* 1993; **9:** 298–304.

3 Marshall JS, Green AM, Pensky J, Williams S, Zinn A, Carlson DM. Measurement of circulating desialylated glycoproteins and correlation with hepatocellular damage. *J Clin Invest* 1974; **54:** 555–62.

4 Sawamura T, Kawasato S, Shiozaki Y, Sameshima Y, Nakada H, Tashiro Y. Decrease of a hepatic binding protein specific for asialoglycoproteins with accumulation of serum asialoglycoproteins in galactosamine-treated rats. *Gastroenterology* 1981; **81:** 527–33.

5 Kudo M, Todo A, Ikekubo K, Hino M. Receptor index via hepatic asialoglycoprotein receptor imaging: correlation with chronic hepatocellular damage. *Am J Gastroenterol* 1992; **87:** 865–70.

6 Kwon AH, Ha-Kawa SK, Uetsuji S, Inoue T, Matsui Y, Kamiyama Y. Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (99mTc-GSA) liver scintigraphy. *Hepatology* 1997; **25:** 426–9.

7 Hwang EH, Taki J, Shuke N *et al*. Preoperative assessment of residual hepatic functional reserve using 99mTc-DTPA-galactosyl-human serum albumin dynamic SPECT. *J Nucl Med* 1999; **40:** 1644–51.

8 Nanashima A, Yamaguchi H, Shibasaki S *et al*. Relationship between indocyanine green test and technetium-99m galactosyl serum albumin scintigraphy in patients scheduled for hepatectomy: clinical evaluation and patient outcome. *Hepatol Res* 2004; **28:** 184–90.

9 Ebata T, Kamiya J, Nishio H, Nagasaka T, Nimura Y, Nagino M. The concept of perihilar cholangiocarcinoma is valid. *Br J Surg* 2009; **96:** 926–34.

10 Das BC, Isaji S, Kawarada Y. Analysis of 100 consecutive hepatectomies: risk factors in patients with liver cirrhosis or obstructive jaundice. *World J Surg* 2001; **25:** 266–73.

11 Kubota K, Makuuchi M, Kusaka K *et al*. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997; **26:** 1176–81.

12 Kawamura H, Kamiyama T, Nakagawa T *et al*. Preoperative evaluation of hepatic functional reserve by converted ICGR15 calculated from Tc-GSA scintigraphy. *J Gastroenterol Hepatol* 2008; **23:** 1235–41.

13 Ikai I, Kudo M, Arii S *et al*. Report of the 18th follow-up survey of primary liver cancer in Japan. *Hepatol Res* 2010; **40:** 1043–59.

14 Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg* 2006; **243:** 364–72.

15 Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S. The use of indocyanine green in the measurement of

hepatic blood flow and as a test of hepatic function. *Clin Sci* 1961; **21:** 43–57.
16 Leevy CM, Mendenhall CL, Lesko W, Howard MM. Estimation of hepatic blood flow with indocyanine green. *J Clin Invest* 1962; **41:** 1169–79.
17 Fujioka H, Kawashita Y, Kamohara Y *et al*. Utility of technetium-99m-labeled-galactosyl human serum albumin scintigraphy for estimating the hepatic functional reserve. *J Clin Gastroenterol* 1999; **28:** 329–33.
18 Mimura T, Hamazaki K, Sakai H, Tanaka N, Mimura H. Evaluation of hepatic functional reserve in rats with obstructive jaundice by asyaloglycoprotein receptor. *Hepatogastroenterology* 2001; **48:** 777–82.
19 Kokudo N, Vera DR, Tada K *et al*. Predictors of successful hepatic resection: prognostic usefulness of hepatic asialoglycoprotein receptor analysis. *World J Surg* 2002; **26:** 1342–7.
20 Yachida S, Wakabayashi H, Okano K, Suzuki Y. Prediction of posthepatectomy hepatic functional reserve by serum hyaluronate. *Br J Surg* 2009; **96:** 501–8.
21 Shimada M, Matsumata T, Adachi E, Itasaka H, Watiyama S, Sugimachi K. Estimation of degree of liver cirrhosis using a fibrosis score; a multivariate analysis of clinical parameters and resected specimens. *Hepatogastroenterology* 1994; **41:** 177–80.
22 Kajiwara E, Akagi K, Azuma K, Onoyama K, Fujishima M. Evidence for an immunological pathogenesis of thrombocytopeniain chronic liver disease. *Am J Gastroenterol* 1995; **90:** 962–6.
23 Kusaka K, Harihara Y, Torzilli G *et al*. Objective evaluation of liver consistency to estimate hepatic fibrosis and functional reserve for hepatectomy. *J Am Coll Surg* 2000; **191:** 47–53.
24 Kamohara Y, Takatsuki M, Hidaka M, Soyama A, Kanematsu T, Eguchi S. 99mTc-Galactosyl sialyl albumin (GSA) scintigram adjusts hepatic resection range in ICG based estimation. *Hepatogastroenterology* 2011; **58:** 2058–61.
25 Kira T, Tomiguchi S, Takahashi M, Yoshimatsu S, Sagara K, Kurano R. Correlation of 99mTc-GSA hepatic scintigraphy with liver biopsies in patients with chronic active hepatitis type C. *Radiat Med* 1999; **17:** 125–30.
26 Dhillon AP, Dusheiko GM. Pathology of hepatitis C virus infection. *Histopathology* 1995; **26:** 297–309.
27 Scheuer PJ, Ashrafzadeh P, Sherlock S, Brown D, Dusheiko GM. The pathology of hepatitis C. *Hepatology* 1992; **15:** 567–71.
28 Lefkowitch JH, Schiff ER, Davis GL *et al*. Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. The Hepatitis Interventional Therapy Group. *Gastroenterology* 1993; **104:** 595–603.
29 Kim YK, Nakano H, Yamaguchi M *et al*. Prediction of postoperative decompensated liver function by technetium-99m galactosyl-human serum albumin liver scintigraphy in patients with hepatocellular carcinoma complicating chronic liver disease. *Br J Surg* 1997; **84:** 793–6.
30 Loehrer AP, House MG, Nakeeb A, Kilbane EM, Pitt HA. Cholangiocarcinoma: are North American surgical outcomes optimal? *J Am Coll Surg* 2013; **216:** 192–200.
31 Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg* 2010; **97:** 1260–8.