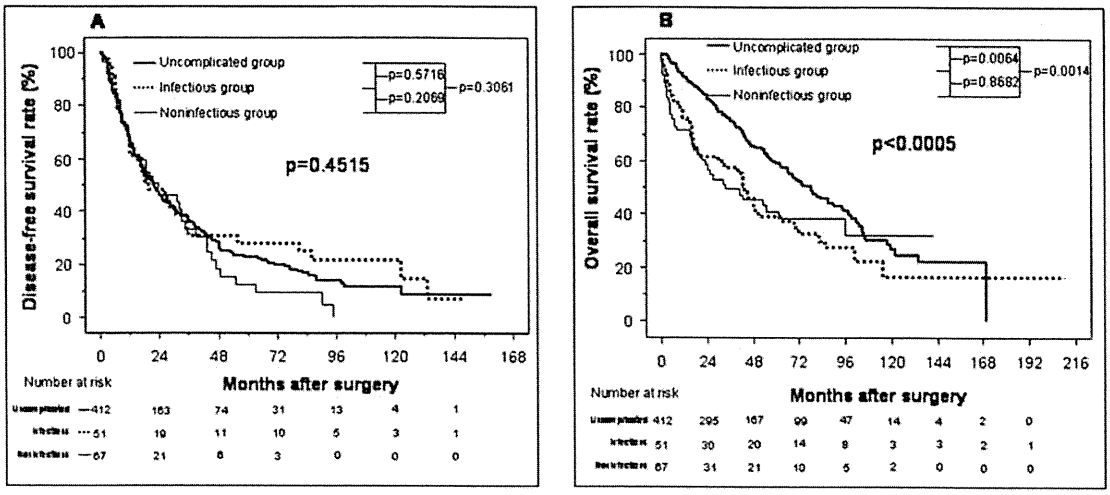

FIGURE 1 Disease-free survival and overall survival. **(A)** Comparison of disease-free survival after resection of HCC among patients classified into a group without complications (uncomplicated group, thick unbroken line), a group with infectious complications (infectious group, dotted line), and a group with non-infectious complications (non-infectious group, thick unbroken line). **(B)** Comparison of overall survival after resection of HCC among patients classified into a group without complications (uncomplicated group, thick unbroken line), a group with infectious complications (infectious group, dotted line) and a group with non-infectious complications (non-infectious group, thick unbroken line). Although the disease-free survival rates of the three groups were not significantly different, overall survival showed significant differences ($p<0.0005$). The number of patients at risk is shown below each graph.

Multivariate analysis identified two significant factors for infectious complications, which were a longer operating time and bile leakage (**Table 4**). It is important to develop ways to decrease the incidence of bile leakage regardless of the operating time and to decrease postoperative infection such as intra-abdominal abscess related to bile leakage when it occurs. Postoperative bile leakage still represents a challenging problem, especially in patients undergoing major hepatectomy, since it is associated with serious complications such as sepsis or liver failure (32). The objective of a bile leak test is to detect inadequately closed bile duct stumps on the cut surface of the liver. However, it has been reported that an intraoperative bile leak test cannot completely exclude the possibility of postoperative bile leakage, because leaks can also occur from small ducts that are not in communication with the main biliary tree (33). Several intraoperative measures for preventing bile leaks have been reported, including the injection of saline (34), methylene blue (35), or ICG (36), intraoperative cholangiography (37), use of an ultrasonic dissector (35), coating the cut surface of the liver with fibrin glue (38) and common bile duct drainage with a T-tube or a thin catheter inserted *via* the cystic duct stump (39), but there is still no standard method. The best way to reduce bile leakage may be to perform surgery with sufficient care. Togo *et al.* reported that if leakage does occur, it is important to prevent an intra-abdominal abscess both by avoiding reflux infection with a closed suction drain and by stopping infection of the cut surface of the liver through the use of synthetic absorbable sutures (40). In this study, infectious complications showed a gradual, but not significant, decrease across the four periods (**Table 1**). On the other hand, multivariate analysis identified three significant factors for non-infectious complications, including a low platelet count, cirrhosis and heavier operative blood loss. To reduce postoperative liver failure, it is important to decrease operative blood loss in cirrhosis patients with a low platelet count. Some previous studies have shown that excessive intraoperative blood loss was a risk factor for postoperative liver failure (41-43). In the present study, operative blood loss and the requirement for blood transfusion both decreased significantly across the four periods (**Table 1**). Because of decreased operative blood loss, non-infectious complications also showed a significant decrease to 4/105 patients (4%) in the fourth period from 10/126 patients (8%), 19/118 patients (16%), and, 34/181 patients (19%) in the third, second and first periods, respectively (**Table 1**).

This study also showed that postoperative infectious and non-infectious complications influenced the overall survival rate, although disease-free survival was not significantly different (**Figure 1**). We previously reported that the prognosis of HCC patients after hepatectomy was influenced by their liver function (44), which affects the ability to offer various treatments. The longer overall survival of the group without complications may be related to the fact that their liver function was better than that of the group with non-infectious complications (**Table 5**). In fact, comparison of clinical variables between the two groups indicated that the liver function of the complication-free group was much better than of the group with non-infectious complications. On the other hand, preoperative liver function did not different between the group with infectious complications and that without complications

(Table 3). The impact of postoperative morbidity on the long-term outcome after cancer surgery has recently been investigated. A study analyzing data from the National Surgical Quality Improvement Program demonstrated that postoperative morbidity was associated with worse long-term survival after selected major operations (45) and a negative impact of postoperative morbidity on the long-term outcome has also been documented after surgery for head and neck cancer (46), colorectal cancer (47) and esophageal cancer (48). The precise mechanism by which postoperative morbidity influences the long-term outcome of cancer remains to be elucidated. Major surgery causes a systemic inflammatory response and immunosuppression (49), which could be exacerbated by postoperative morbidity. There has been speculation that prolonged systemic inflammation and immunosuppression associated with postoperative morbidity could promote the survival and subsequent growth of tumor micrometastases. Thus, the occurrence of infectious complications may have an influence on overall survival after surgical resection.

In conclusion, we found that a longer operating time and bile leakage were risk factors for infectious complications, while a low platelet count, cirrhosis and greater operative blood loss were risk factors for non-infectious complications in HCC patients undergoing potentially curative resection. To achieve a zero morbidity rate, it is important to avoid bile leakage and minimize blood loss during surgery for HCC in patients with cirrhosis.

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INVITED REVIEW ARTICLE

Usefulness of Tc-99m-GSA scintigraphy for liver surgery

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Abstract Postoperative mortality remains high after hepatectomy compared with other types of surgery in patients who have cirrhosis or chronic hepatitis. Although there are several useful perioperative indicators of liver dysfunction, no standard markers are available to predict postoperative liver failure in patients with hepatocellular carcinoma (HCC) undergoing hepatectomy. The best preoperative method for evaluating the hepatic functional reserve of patients with HCC remains unclear, but technetium-99m diethylenetriamine pentaacetic acid galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy is a candidate. ^{99m}Tc-GSA is a liver scintigraphy agent that binds to the asialoglycoprotein receptor, and can be used to assess the functional hepatocyte mass and thus determine the hepatic functional reserve in various physiological and pathological states. The maximum removal rate of ^{99m}Tc-GSA (GSA-Rmax) calculated by using a radiopharmacokinetic model is correlated with the severity of liver disease. There is also a significant difference of GSA-Rmax between patients with chronic hepatitis and persons with normal liver function. Regeneration of the remnant liver and recurrence of hepatitis C virus infection in the donor organ after living donor liver transplantation have also been investigated by ^{99m}Tc-GSA scintigraphy. This review discusses the usefulness of ^{99m}Tc-GSA scintigraphy for liver surgery.

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Keywords GSA-Rmax · Hepatocellular carcinoma · Hepatectomy · Living donor liver transplantation · Regeneration · Hepatitis C virus

Introduction

Ashwell and Morell [1] demonstrated the existence of a hepatic receptor for asialoglycoprotein (ASGP) during investigation of ceruloplasmin metabolism. They found that ceruloplasmin molecules lacking a sialic acid residue disappeared rapidly from the circulation and were taken up by hepatocytes [2]. The ASGP receptor is only expressed by mammalian hepatocytes, and is almost always expressed on the sinusoidal and lateral surfaces of hepatocytes in the normal liver [3]. Sawamura et al. [4] reported that a decrease of ASGP receptors led to accumulation of ASGP in the serum of galactosamine-treated rats. Expression of this receptor is also decreased in patients with chronic liver disease [5]. Technetium-99m diethylenetriamine pentaacetic acid galactosyl human serum albumin (^{99m}Tc-GSA) is a liver scintigraphy agent that binds to the ASGP receptor on hepatocytes [6]. The maximum removal rate of Tc-GSA (GSA-Rmax) calculated with a radiopharmacokinetic model is reported to decrease as liver disease becomes more severe, and there is also a significant difference of GSA-Rmax between patients with chronic hepatitis and persons with normal liver function [7]. Because this agent binds to hepatocytes for a long period, the distribution of the functioning hepatocyte mass can be assessed by performing single-photon emission computed tomography (SPECT) with Tc-GSA [8]. Hepatic abnormalities detected by ^{99m}Tc-GSA scintigraphy show a good correlation with histologic abnormalities, especially steatosis and fibrosis or necrosis in patients with fatty liver or chronic hepatitis

[9, 10]. This review focuses on the use of ^{99m}Tc-GSA to measure preoperative hepatic function in HCC patients undergoing hepatectomy, as well as the hepatic functional reserve in donors and recipients after living donor liver transplantation (LDLT), as reported previously by Kaibori et al. [11–13].

Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [14]. Although the majority still occurs in Asia and Africa, the incidence and mortality rate of HCC have recently been increasing in North America and Europe [15, 16]. In Japan, most HCCs are associated with chronic hepatitis and liver cirrhosis induced by hepatitis B or hepatitis C virus infection. Due to advances in perioperative management, anesthesia, and operative techniques, the performance of hepatectomy for HCC has become more common. However, the postoperative mortality rate remains high in patients who have cirrhosis or chronic hepatitis compared with that for other types of surgery. In fact, the mortality rate after major hepatectomy is between 5 and 21% for patients with cirrhosis [17–21]. The postoperative course does not always proceed as predicted because of various intraoperative stresses, including blood loss and ischemia, so preoperative evaluation of hepatic function in HCC patients undergoing hepatectomy is essential. Several perioperative variables, including the galactose elimination capacity [22], preoperative portal pressure [23], ^{99m}Tc-GSA liver scintigraphy [7], indocyanine green (ICG) clearance test [24, 25], amino acid clearance test [26], and aminopyrine breath test [27], are useful for identifying hepatic impairment in patients with HCC undergoing hepatectomy. Some studies have indicated that ICG clearance (expressed as the percentage of ICG retained at 15 min) is the best preoperative test for evaluation of the hepatic functional reserve in HCC patients [24, 25]. However, discrepancies between ICG clearance and liver histology are occasionally seen, which are thought to mainly depend on the effective hepatic blood flow resulting from intrahepatic and extrahepatic shunts. ICG has been considered an ideal substance for kinetic analysis of hepatic function since it is nontoxic at clinical doses and is reported to not undergo extrahepatic removal, intrahepatic conjugation, or enterohepatic circulation. ICG is a near-infrared fluorescent dye that was approved by the US Food and Drug Administration for cardiovascular and liver function diagnostic testing. There have also been recent reports about the usefulness of ICG for intraoperative fluorescence imaging to detect sentinel nodes in patients with breast cancer or gastric cancer [28, 29]. We and others have found that HCC shows very strong fluorescence in patients who have been given ICG several days before surgery for routine preoperative assessment of liver function (Fig. 1) [30, 31]. Therefore, we came to doubt that the ICG clearance test is the best procedure for evaluating preoperative hepatic function, because not only did ICG dye show intrahepatic conjugation, but it also accumulated in the HCC nodules.

The ICGR15 test and ^{99m}Tc-GSA scintigraphy were performed in 384 patients with HCC prior to liver resection at our institution. Table 1 shows the correlations between GSA-Rmax or ICGR15 and other laboratory test results in HCC patients with a preoperative ICGR15 $< 20\%$. There were significant correlations between GSA-Rmax or ICGR15 and other laboratory values. However, only GSA-Rmax, and not ICGR15, was significantly correlated with some of the laboratory tests in HCC patients with a preoperative ICGR15 $\geq 20\%$ (Table 2). Thus, both ^{99m}Tc-GSA scintigraphy and ICG clearance may be useful

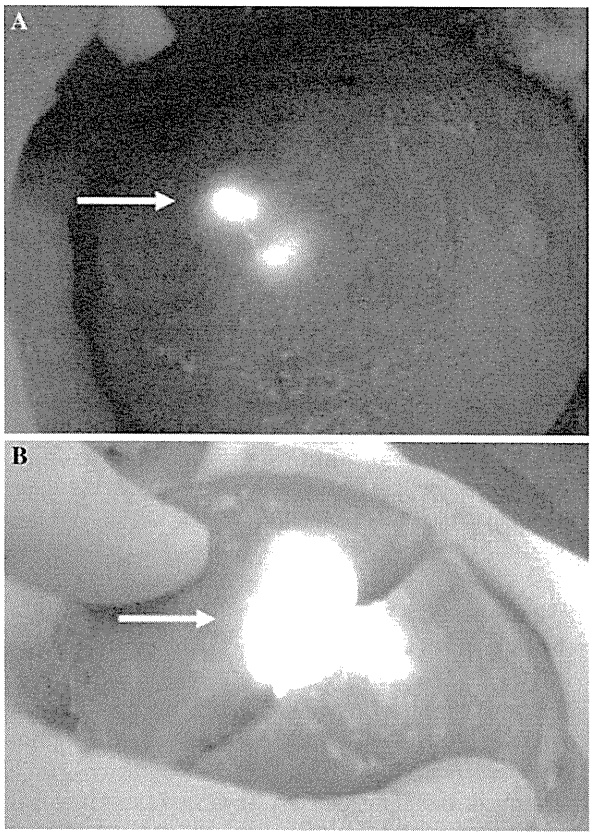

Fig. 1 Indocyanine green fluorescence imaging in a 62-year-old woman who underwent hepatectomy for HCC. **a** Intraoperative ICG fluorescence imaging shows a strong signal in the primary HCC nodule (*thin arrow*). **b** Postoperative ICG fluorescence imaging shows a strong signal in the primary tumor nodule in the liver slice (*thin arrow*)

Table 1 Correlations between GSA-Rmax or ICGR15 and other laboratory tests in hepatocellular carcinoma patients with ICGR15 <20%

Test	GSA-Rmax			ICGR15		
	n	*r*	*P* value	*n*	*r*	*P* value
ICGR15	236	−0.397	**<0.0001**			
AST	236	−0.362	**<0.0001**	236	0.199	**0.0021**
Total bilirubin	236	−0.291	**<0.0001**	236	0.356	**<0.0001**
Platelet count	236	0.48	**<0.0001**	236	−0.328	**<0.0001**
Albumin	236	0.09	0.17	236	−0.035	0.5961
Cholinesterase	236	0.413	**<0.0001**	236	−0.222	**0.0006**
Prothrombin time	234	0.183	**0.0049**	234	−0.159	**0.0151**
Type IV collagen 7S	119	−0.231	**0.0112**	119	0.209	**0.0225**
Hyaluronate acid	124	−0.299	**0.0007**	124	0.060	0.5091

Significant differences are shown in bold

ICGR15 indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *GSA-Rmax* regional maximum removal rate of technetium-99m galactosyl human serum albumin

Table 2 Correlations between GSA-Rmax or ICGR15 and other laboratory tests in hepatocellular carcinoma patients with ICGR15 ≥ 20%

Test	GSA-Rmax			ICGR15		
	n	*r*	*P* value	*n*	*r*	*P* value
ICGR15	148	−0.107	0.1969			
AST	148	−0.137	0.098	148	−0.044	0.6001
Total bilirubin	148	−0.12	0.1474	148	0.283	**0.0005**
Platelet count	148	0.303	**0.0002**	148	−0.505	0.5507
Albumin	148	0.413	**<0.0001**	148	−0.125	0.1308
Cholinesterase	148	0.496	**<0.0001**	148	−0.117	0.1557
Prothrombin time	148	0.375	**<0.0001**	148	−0.067	0.4204
Type IV collagen 7S	93	−0.306	**0.0027**	93	0.196	0.0593
Hyaluronate acid	94	−0.316	**0.0018**	94	0.133	0.2009

Significant differences are shown in bold

ICGR15 indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *GSA-Rmax* regional maximum removal rate of technetium-99m galactosyl human serum albumin

procedures for preoperative evaluation of the hepatic functional reserve in patients with HCC.

Hyaluronate/GSA-Rmax ratio as a predictor of postoperative liver failure

The serum levels of type IV collagen and hyaluronic acid (HA) were measured in 191 patients with HCC prior to liver resection, and ^{99m}Tc-GSA scintigraphy was also performed. In brief, 3 mg of Tc-GSA (185 MBq; Nihon Medi-Physics, Nishinomiya, Japan) was injected into an antecubital vein as a bolus dose. Images were obtained as 10-s frames for 15 min after injection using a gamma camera with a large field of view (GSA-7100A/DI; Toshiba, Tokyo) and a high-resolution, parallel-hole collimator centered over the liver and precordium. Then GSA-Rmax was calculated by using a radiopharmacokinetic model [7].

Liver failure was defined by the postoperative occurrence of any of the following: encephalopathy associated with hyperbilirubinemia (total bilirubin >5 mg/dl) for more than 5 days, intractable pleural effusion or ascites (requiring diuretics, thoracocentesis, or abdominal paracentesis on 2 or more occasions, or continuous drainage), or variceal bleeding [31, 32]. Logistic regression analysis was performed and odds ratios (ORs) were calculated to estimate the relative risk of postoperative liver failure. In these analyses, $P < 0.05$ was considered to indicate statistical significance.

Postoperative liver failure occurred in 16 patients (encephalopathy associated with hyperbilirubinemia in 3

Table 3 Risk factors for hepatic failure after resection of hepatocellular carcinoma calculated by multivariate analysis

GSA-Rmax regional maximum removal rate of technetium-99m-galactosyl human serum albumin, *HA* hyaluronic acid, *AFP* α-fetoprotein, *CI* confidence interval

Variable	Odds ratio	95% CI	*P* value
Albumin < 3.7 g/dl	4.12	0.85–20.00	0.0796
Total bilirubin ≥ 0.7 mg/dl	4.13	0.44–38.60	0.2134
GSA-Rmax < 0.475 mg/min	0.17	0.01–2.92	0.2229
Type IV collagen 7S ≥ 6.0 ng/ml	0.13	0.01–1.27	0.0792
HA ≥ 150 ng/ml	1.54	0.13–18.81	0.7338
Type IV collagen 7S/GSA-Rmax ≥ 15 mg min/dl	7.65	0.31–36.14	0.2116
HA/GSA-Rmax ≥ 500 mg min/dl	23.60	1.91–62.09	0.0138
AFP ≥ 17 ng/ml	4.14	0.78–21.99	0.0951

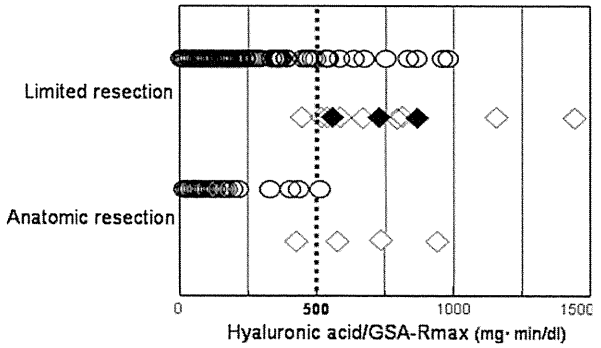

Fig. 2 Relations among the HA/GSA-Rmax ratio, surgical procedure, and occurrence of liver failure. *Circles* patients without postoperative liver failure. *Open diamonds* patients with postoperative liver failure. *Closed diamonds* patients who died of postoperative liver failure

patients, refractory massive ascites or pleural effusion in 12 patients, and variceal bleeding in 1 patient), and three of them died of liver failure in hospital. The ORs of possible risk factors for postoperative liver failure calculated by univariate analysis were as follows: age (OR = 3.56), Child-Pugh class B (OR = 3.33), ICGR15 (OR = 3.25), serum albumin (OR = 6.21), total bilirubin (OR = 10.74), cholinesterase (OR = 3.40), platelet count (OR = 4.93), AST (OR = 4.80), GSA-Rmax (OR = 8.13), type IV collagen 7S (OR = 3.97), HA (OR = 11.85), type IV collagen 7S/GSA-Rmax ratio (OR = 18.08), HA/GSA-Rmax ratio (OR = 21.49), AFP (OR = 4.54), microscopic invasion of the portal vein and/or hepatic vein (OR = 3.65), and cirrhosis (OR = 3.12). According to multivariate analysis, an HA/GSA-Rmax ratio ≥500 mg min/dl (OR = 23.60; 95% CI = 1.91–62.09; $P = 0.0138$) was the only independent predictor of postoperative liver failure (Table 3). The HA/GSA-Rmax ratio was significantly higher in patients with postoperative liver failure than in patients without it after either anatomic resection or limited resection (both $P < 0.0001$, Fig. 2). Following limited resection, all of the patients who died of postoperative liver failure had an HA/GSA-Rmax ratio ≥500 mg min/dl (Table 4).

Other reported risk factors for postoperative liver failure include type IV collagen 7S [33, 34], HA [35, 36], and GSA-Rmax [7], but these parameters were not found to be significant in our study. To reduce postoperative liver failure, various measures of the hepatic functional reserve should be assessed before surgery, including tests of both parenchymal and nonparenchymal liver function. Limited liver resection has been recommended for the treatment of HCC in patients with cirrhosis [37, 38]. Three patients with a HA/GSA-Rmax ratio ≥500 mg min/dl who underwent limited resection died of postoperative liver failure in our study. Our findings indicate that the HA/GSA-Rmax ratio is a useful predictor of the risk of postoperative liver failure and a ratio ≥500 mg min/dl is a relative contraindication to hepatectomy.

Liver regeneration in donors evaluated by ^{99m}Tc-GSA scintigraphy after living donor liver transplantation

When living donor liver transplantation (LDLT) is performed, steatosis is one of the risk factors for graft dysfunction and severe macrovesicular steatosis is an absolute contraindication to transplantation [39]. Hepatic steatosis is also reported to affect the postoperative recovery of the donor [40]. However, the extent of macrovesicular steatosis has been reported to decrease immediately after partial hepatectomy, and although early liver regeneration is impaired after partial hepatectomy in patients with mild macrovesicular steatosis, long-term regeneration is reported to be normal [41]. Thus, whether mild hepatic steatosis influences regeneration of the donor's liver after partial hepatectomy is still controversial. Accordingly, we employed ^{99m}Tc-GSA scintigraphy to assess the impact of steatosis on regeneration and function of the remnant donor liver after hepatectomy.

A total of 14 patients underwent LDLT at our institution and 12 living donors with complete ^{99m}Tc-GSA liver scintigraphy data and histological data from intraoperative liver biopsy specimens were investigated. The liver-to-spleen CT attenuation ratio (*L/S* ratio) was measured on

Table 4 Changes of serum HCV RNA, HAI, METAVIR score, and liver function parameters after transplantation

Time (mo)	Pre	1	3	6	12
Patient 1					
HCV RNA (IU/ml)	1.5×10^6	1.5×10^6	3.2×10^6	3.8×10^6	6.8×10^6
HAI score	ND	ND	3	5	10
METAVIR score	ND	ND	A1/F0	A2/F1	A2/F2
Hyaluronic acid (ng/ml)	912	ND	229	265	306
ALT (U/L)	39	93	62	26	37
Platelet count (10^4/ml)	6.1	16.4	9.3	14.2	8.0
Prothrombin time (%)	50	72	77	84	75
Total bilirubin (mg/dl)	6.1	1.3	1.6	1.6	1.5
Patient 2					
HCV RNA (IU/ml)	0.3×10^6	0.6×10^6	3.7×10^6	3.8×10^6	3.5×10^6
HAI score	ND	ND	2	4	4
METAVIR score	ND	ND	A1/F0	A1/F0	A1/F1
Hyaluronic acid (ng/ml)	378	ND	136	76	69
ALT (U/L)	36	90	115	128	104
Platelet count (10^4/ml)	5.7	6.6	12.2	8.6	9.1
Prothrombin time (%)	49	89	100	91	94
Total bilirubin (mg/dl)	3.6	8.0	1.6	0.9	0.6
Patient 3					
HCV RNA (IU/ml)	0.4×10^6	1.3×10^6	7.0×10^6	4.9×10^6	0.5×10^{6a}
HAI score	ND	ND	4	10	22[a]
METAVIR score	ND	ND	A1/F1	A2/F2	A3/F4[a]
Hyaluronic acid (ng/ml)	218	ND	523	411	ND
ALT (U/L)	47	85	53	100	91[a]
Platelet count (10^4/ml)	4.0	7.2	5.4	4.9	4.6[a]
Prothrombin time (%)	70	88	83	79	52[a]
Total bilirubin (mg/dl)	2.4	2.5	2.2	2.7	24.0[a]
Patient 4					
HCV RNA (IU/ml)	0.7×10^5	2.5×10^6	6.1×10^6	0.3×10^4	0.4×10^6
HAI score	ND	ND	3	3	4
METAVIR score	ND	ND	A1/F0	A1/F0	A1/F1
Hyaluronic acid (ng/ml)	300	ND	82	103	94
ALT (U/L)	40	17	43	46	18
Platelet count (10^4/ml)	2.5	8.5	9.6	7.2	8.7
Prothrombin time (%)	37	73	87	71	87
Total bilirubin (mg/dl)	3.6	1.6	1.7	1.3	1.0

[a] This was determined at 8 months after transplantation. Treatment with a combination of interferon plus ribavirin was initiated at 7 months after transplantation

HAI histologic activity index, *A* activity score, *F* fibrosis score, *ALT* alanine aminotransferase, *ND* not determined

noncontrast CT scans as an index of hepatic steatosis, as described previously [42]. Liver biopsy specimens obtained during surgery were assessed for macrovesicular steatosis, which was classified as absent (0%), mild (<30%), moderate (30–60%), or severe (>60%). The median *L/S* ratio for each of these histological categories was 1.20, 1.12, 1.01, and 0.90, respectively, with the optimum *L/S* ratio for prediction of mild or moderate hepatic steatosis being 1.20 and 1.10, respectively. The donors were classified into 2 groups with or without mild hepatic steatosis according to the *L/S* ratio, i.e., 6 donors who had an *L/S* ratio $\geq$1.20 (mean $\pm$ standard deviation, 1.35 $\pm$ 0.03) were assigned to the control group, whereas the other 6 donors who had an *L/S* ratio <1.20 (mean $\pm$ standard deviation, 1.10 $\pm$ 0.11) were assigned to the fatty liver group. Informed consent was obtained from all of the donors. To perform ^{99m}Tc-GSA scintigraphy, 3 mg of Tc-GSA (185 MBq, Nihon Medi-Physics,

Nishinomiya, Japan) was injected into an antecubital vein as a bolus dose. Images were obtained as 10-s frames for 15 min after injection using a gamma camera with a large field of view (GCA-7100A/DI, Toshiba, Tokyo, Japan) and a high-resolution, parallel-hole collimator centered over the liver and precordium. Two quantitative indices were calculated from the time-activity curves thus obtained. The blood clearance index was calculated as the ratio of uptake by the heart at 15 min to that at 3 min (HH15), and the hepatic accumulation index was calculated as the ratio of uptake by the liver alone to that of uptake by the liver plus heart at 15 min (LHL15) [43]. Then these two indices were used to calculate the hepatic uptake ratio corrected by blood clearance (LHL/HH) as a parameter of the hepatic functional reserve. Taking the values of the LHL/HH ratio, GSA-Rmax, and computed tomographic liver volume (CT-LV) before partial hepatectomy as 100%, the results obtained at 1, 3, 6, and 12 months after surgery were expressed as a percentage of the preoperative values. This revealed that the CT-LV of the fatty liver group and the control group was respectively 72 ± 3 and 78 ± 8% of the baseline value at 1 month after partial hepatectomy, whereas it was 79 ± 8 and 81 ± 12% at 3 months, 82 ± 5 and 83 ± 6% at 6 months, and 85 ± 5 and 90 ± 9% at 12 months (Fig. 3a). There were no significant differences between the two groups at any time.

The fatty liver group had a significantly lower LHL/HH ratio and GSA-Rmax than the control group at both 6 and 12 months after hepatectomy (Fig. 3b, c). The LHL/HH ratio and GSA-Rmax were decreased at 1 month in both groups, but these values returned more rapidly to baseline in the control group and GSA-Rmax even became higher than before hepatectomy. In the fatty liver and control groups, the LHL/HH ratio and GSA-Rmax were respectively 79 ± 7 versus 95 ± 8% and 83 ± 2 versus 125 ± 24% of baseline at 1 year after surgery.

Recently, LDLT has become an alternative to cadaveric liver transplantation as a means of overcoming the perpetual shortage of donor organs. The unique ability of the liver to regenerate completely after resection makes this approach possible. A recent massive increase in the number of partial liver transplant procedures has renewed interest in liver regeneration. The process of regeneration ceases after the liver has achieved 75–95% of its original weight. Pomfret et al. [44] reported that regeneration achieved an average of 84 ± 9.0% of the original liver volume by 1 year after surgery. Humar et al. [45] reported that recipients showed a greater increase of liver volume than their living donors, with the donor livers reaching 79% of their original volume by 3 months, postoperatively. We previously reported that the regenerated liver volume estimated by CT volumetry was significantly correlated with that estimated by ^{99m}Tc-GSA after partial

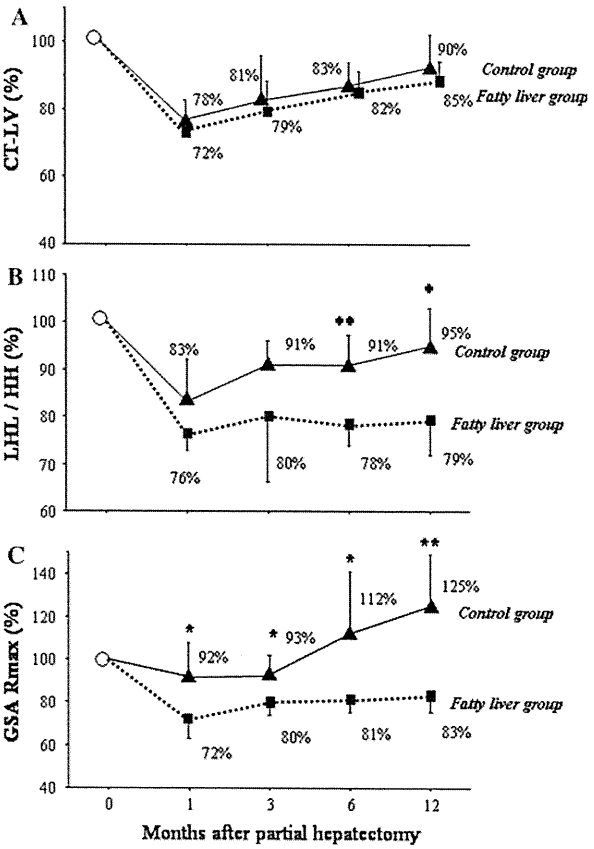

Fig. 3 Changes of CT-LV, LHL/HH, and GSA-Rmax after partial hepatectomy. **a** CT-LV, **b** LHL/HH, and **c** GSA-Rmax. Each value obtained before hepatectomy was set at 100%, and the values obtained at 1, 3, 6, and 12 months after surgery were expressed as percentages of the preoperative value

hepatectomy for benign and malignant tumors [46]. Our study also showed that normal livers (control group) underwent rapid regeneration and reached 90 ± 9% of the preoperative volume by 1 year after hepatectomy (Fig. 4a). A certain amount of redundancy built into the liver may explain why regeneration tends to cease before the pretransplant volume is reached. In our study, the LHL/HH ratio and GSA-Rmax were decreased at 1 month after surgery in both groups, but both parameters returned to prehepatectomy levels by 1 year in the control group, whereas the fatty liver group had a significantly lower LHL/HH ratio and GSA-Rmax at 6 and 12 months after hepatectomy (Fig. 4b, c). These results indicate that regeneration of functioning hepatocytes is impaired when the donor has mild hepatic steatosis. Our findings also suggest that careful management of major or minor morbidities is required during the regeneration period after partial hepatectomy in donors with mild hepatic steatosis.

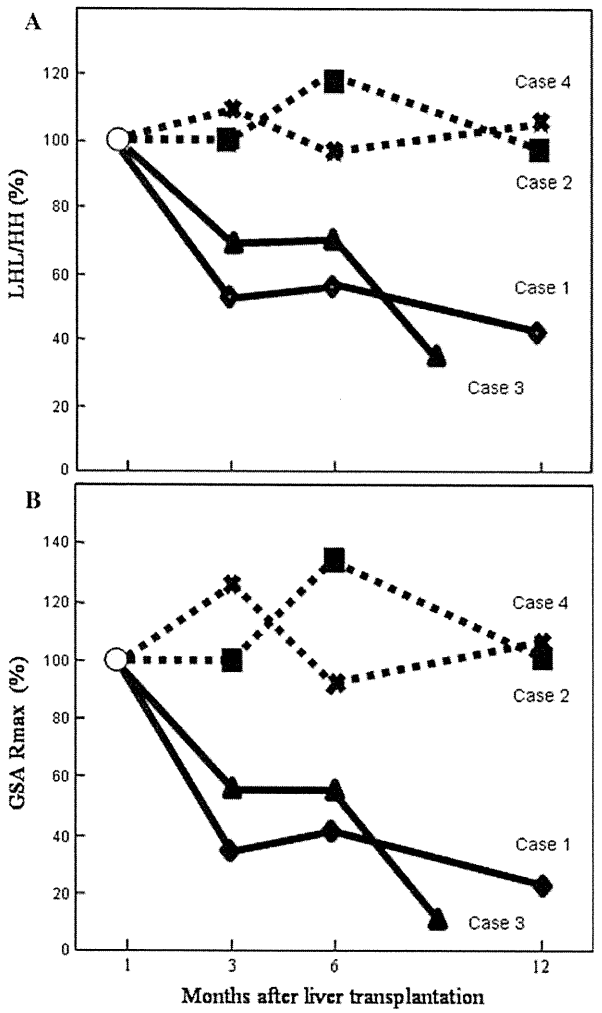

Fig. 4 Changes of LHL/HH and GSA-Rmax after transplantation. **a** LHL/HH, **b** GSA-Rmax. The values of LHL/HH and GSA-Rmax obtained at 1 month after transplantation were set as 100%, and the values obtained at 3, 6, and 12 months were expressed as a percentage of the 1-month values

Recurrent hepatitis C after living donor liver transplantation detected by ^{99m}Tc-GSA liver scintigraphy

Hepatitis C virus (HCV)-related liver disease is the leading indication for liver transplantation [47]. Recurrent hepatitis that causes cirrhosis or graft loss respectively occurs in approximately 20 and 10% of patients within 5 years after transplantation [48, 49], and the risk of these complications increases over time [50]. Because the number of liver transplant recipients with recurrent and severe hepatitis C has continued to increase, various HCV treatment strategies have been explored. At present, mainstream therapy involves providing treatment for patients with histologically progressive liver disease after transplantation. However, the overall response rate achieved with a combination of interferon plus ribavirin is approximately 20%, indicating that this approach is unlikely to be successful in the majority of patients [51]. Unfortunately, the optimum timing for initiation of treatment and the dosages of interferon and ribavirin required to achieve viral eradication after liver transplantation have not yet been established. Although liver biopsy is essential to determine the need for interferon and ribavirin therapy, this is an invasive procedure, particularly in the early post-transplant period. We investigated whether recurrent hepatitis C could be detected by ^{99m}Tc-GSA scintigraphy after LDLT.

A total of 14 patients underwent LDLT at our institution. Among them, six patients had decompensated cirrhosis because of hepatitis caused by HCV infection. Two of these six patients did not undergo ^{99m}Tc-GSA scintigraphy after transplantation, and were excluded. The remaining 4 patients were reviewed retrospectively after informed consent was obtained. Before surgery, the four patients were shown to have HCV genotype 1b. All patients tolerated surgery well without significant intraoperative or early postoperative complications and recovered uneventfully. They received a standard primary immunosuppression protocol consisting of tacrolimus and corticosteroids [52]. All four patients underwent laboratory tests and assessment of graft function by ^{99m}Tc-GSA scintigraphy at 1, 3, 6, and 12 months after transplantation. Percutaneous liver biopsy was also performed at 3, 6, and 12 months after surgery. The diagnosis of hepatitis was based on the histologic activity index (HAI) [53] and the METAVIR [54, 55] score, which demonstrates the grade of necroinflammation and stage of fibrosis. Taking the LHL/HH ratio and GSA-Rmax at 1 month after transplantation as 100%, the values at 3, 6, and 12 months were expressed as a percentage of the 1-month values. Table 3 shows the changes of serum HCV RNA, HAI, METAVIR score, and liver function parameters after transplantation in each patient. HCV RNA was detected in the serum at 3 months after transplantation in all four patients. In patient 1, HCV RNA was twofold higher at 12 months compared with its level at 6 months. In patients 3 and 4, serum HCV RNA was decreased at 6 and 8 months compared with the level at 3 months. The levels of hyaluronic acid and alanine aminotransferase (ALT), as well as the prothrombin time and platelet count, showed little change after transplantation in all of the patients. Although total bilirubin was decreased at 6 months in patients 2 and 4, it did not decrease in patients 1 and 3. At 6 months after transplantation, the HAI score determined by liver biopsy was 5 in patient 1 and 10 in patient 3. The METAVIR activity score (A) was 2 and the fibrosis score (F) was 1 in patient 1, whereas the

scores were A2/F2 in patient 3. In patient 1, the HAI and METAVIR score respectively showed an increase to 10 and A2/F2 at 12 months after transplantation, and recurrence of HCV infection was also indicated by other histologic findings. Accordingly, the patient was treated with a combination of interferon plus ribavirin. In patient 3, treatment with a combination of interferon plus ribavirin was initiated at 7 months after transplantation, but the HAI and METAVIR score respectively increased to 22 and A3/F4 at 8 months. The liver histology was compatible with fibrosing cholestatic hepatitis and the patient died of progressive hepatic failure at 10 months after transplantation. In patients 2 and 4, recurrence of HCV infection was not detected by histologic examination. The LHL/HH ratio and GSA-Rmax showed little change after transplantation in these patients (Fig. 4). In patient 1, however, the LHL/HH ratio and GSA-Rmax both showed a decrease at 3 months after transplantation and subsequently remained at low levels. Both the LHL/HH ratio and GSA-Rmax were decreased at 3 months after transplantation in case 3, and declined further by 8 months.

This study showed that changes of ^{99m}Tc-GSA scintigraphy were better correlated with the stage of hepatic fibrosis than with the grade of necroinflammation (as indicated by the METAVIR score). We previously reported that the results of ^{99m}Tc-GSA scintigraphy were well correlated with the HAI score, especially that for fibrosis, and suggested that scintigraphy may be useful for noninvasive preoperative evaluation of hepatic fibrosis [7]. Because hepatic fibrosis causes the loss of normal hepatocytes and reduces the number of receptors available to bind ^{99m}Tc-GSA, scintigraphy can indicate the pathological stage of chronic hepatic parenchymal damage. In our study, recurrent HCV infection was confirmed by histologic examination at 6 and 12 months after transplantation in two patients. The decrease of the LHL/HH ratio and GSA-Rmax at 3 months after transplantation in these two patients suggested an early effect of recurrent hepatitis C on the graft before changes of other parameters occurred. It may be reasonable to commence antiviral therapy on the basis of such findings. In patients with recurrent hepatitis C after LDLT, accurate evaluation of hepatic functional reserve is very important for selection of treatment and estimation of the prognosis, but a standard method has not been established. Although needle biopsy is currently essential to determine the indications for interferon and ribavirin therapy, this test is quite invasive in the early posttransplantation period. Thus, ^{99m}Tc-GSA liver scintigraphy may have a potential role as a noninvasive method of evaluating graft functional reserve, but its value will need to be confirmed by further investigations.

Conclusion

To reduce postoperative liver failure, preoperative planning should employ various tests to assess the hepatic functional reserve, including tests of both parenchymal and nonparenchymal liver function. The HA/GSA-Rmax ratio can predict liver failure after hepatectomy, and a ratio ≥500 mg min/dl is a relative contraindication to liver resection. After LDLT, ^{99m}Tc-GSA liver scintigraphy may be useful for evaluating the regeneration of functioning hepatocytes. Because we found that donors with mild hepatic steatosis showed impaired liver regeneration at 1 year after partial hepatectomy, management of such donors requires more care. In liver transplant recipients with HCV, a decrease of GSA-Rmax at 3 months after transplantation suggests recurrent HCV infection of the graft, and ^{99m}Tc-GSA liver scintigraphy is a useful noninvasive method for evaluating the graft functional reserve.

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Intraoperative indocyanine green fluorescent imaging for prevention of bile leakage after hepatic resection

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Background. *Bile leakage is a common complication of hepatectomy, and is associated with an increase in sepsis and liver failure. There are no standard preventive methods against bile leakage after hepatic surgery. The aim of the present randomized clinical trial was to evaluate the application of indocyanine green (ICG) fluorescent cholangiography for preventing postoperative bile leakage.*

Methods. *102 patients who underwent hepatic resection without biliary reconstruction were divided into 2 groups. The control group (n = 50) underwent a leak test with ICG dye alone, and the experimental group underwent a leak test with ICG dye, followed by ICG fluorescent cholangiography using the Photodynamic Eye (PDE group, n = 52).*

Results. *Among 42 patients with fluorescence in the PDE group, 25 patients had insufficient closure of bile ducts on the cut surface of the liver, which were closed by suture or ligation. There were 5 patients who developed postoperative bile leakage in the control group versus no bile leakage in the PDE group (10% vs 0%, P = .019).*

Conclusion. *ICG fluorescent cholangiography could detect insufficiently closed bile ducts that could not be identified by a standard bile leak test. ICG fluorescent cholangiography may have useful potential for prevention of bile leakage after hepatic resection. (Surgery 2011;150:91-8.)*

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As a result of improved operative techniques and perioperative care, hepatic surgery has become safer in recent years, and the operative mortality rate has decreased.[1-4] Despite the overall decrease of postoperative complications, however, the incidence of bile leakage has not changed and is reported to range from 3.6% to 33%,[5-13] making it one of the most common complications of hepatic surgery. Bile leakage is associated with an increase of sepsis and liver failure, a greater postoperative mortality rate, and a greater hospital stay.[6] Therefore, it is important to minimize the occurrence of this complication.

Several intraoperative tests for bile leakage have been employed. The advantages of injecting saline include low cost, no toxicity, and no limitations on repetition; however, it is difficult to detect microleakage of saline because the solution is clear.[9] Biliary injection of dyes, such as indocyanine green (ICG)[6,14] and methylene blue,[5,15] has also been recommended for better detection of bile leakage; however, such dyes have the drawback of staining the surrounding tissues, making it difficult to localize precisely multiple leaks. Intraoperative cholangiography is considered to be the gold standard, but exposes the patient and medical staff to radiation and requires C-arm fluoroscopy and additional human resources.[16,17] Li et al[18] and Nadalin et al[19] reported that intraductal injection of 5% fat emulsion is a feasible and sensitive test for bile leakage, the so-called "white test", with no obvious disadvantages. Although its efficacy for decreasing postoperative bile leakage was demonstrated in their prospective cohort study, the "white test" has not been assessed in a randomized study. Thus, the value of intraoperative tests for preventing postoperative bile leakage remains debated.[9,15]

Recently, intraoperative fluorescent angiography has been performed after intravenous injection of ICG to assess the patency of coronary artery bypass grafts.[20-23] Mitsuhashi et al[24] reported that intraoperative fluorescence imaging during hepatobiliary surgery leads to better understanding of the anatomy of the arteries, portal vein, and bile ducts. ICG binds to plasma proteins, and

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protein-bound ICG emits near-infrared light.[25,26] Human bile also contains proteins that can bind with ICG,[27] and Ishizawa et al[28] recently reported that fluorescent images of the biliary tract could be obtained after intrabiliary injection of this dye. We hypothesized that fluorescent cholangiography with ICG is able to detect minor bile leakage from the cut surface of the remnant liver after hepatic resection. Accordingly, the aim of the present randomized clinical trial was to evaluate the application of fluorescent cholangiography for preventing postoperative bile leakage.

MATERIALS AND METHODS

Patients. All patients scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between August 2008 and July 2010 were screened for this study. The inclusion criteria were elective hepatectomy, no bilioenterostomy, adequate cardiopulmonary and renal function, and ability to give written informed consent. Before operation, each patient underwent conventional liver function tests and measurement of the indocyanine green retention rate at 15 min (ICGR15). Hepatitis screening was done by measurement of hepatitis B surface antigen and hepatitis C antibody. Preoperative radiologic assessment always included computed tomography or magnetic reasonance imaging of the chest, abdomen, and pelvis. Intraoperative ultrasonography was performed to confirm the preoperative imaging findings and to assist in planning the operative procedure. Operations were classified according to the Brisbane terminology proposed by Strasberg et al.[29] 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 resection of Couinaud subsegments[30] V-VIII and left hemihepatectomy was resection of subsegments II-IV), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of 2 Couinaud subsegments), or segmentectomy (resection of 1 Couinaud subsegment). All non-anatomic procedures were classified as limited resection, which was done for both peripheral tumors and central tumors. Peripheral tumors and tumors with extrahepatic growth were treated by partial hepatectomy, because this method was 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 closed-suction, silicon drain was positioned in the subphrenic or subhepatic space close to the cut surface of the liver before abdominal wound closure. The drain was brought out through a separate stab wound on the anterior abdominal wall and was connected to a closed system with low suction pressure. The abdominal drain was removed on postoperative day 5 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 either a conventional bile leakage test with ICG dye alone or a test by fluorescent ICG cholangiography using the Photodynamic Eye (PDE). All patients gave written informed consent to participation in the trial and were randomized by the envelope method. Patients were informed of the result of randomization before operation. All operations were performed by the same surgeon, who had experience of over 600 hepatic resections. The protocol for this study was approved by the institutional ethics committee.

Surgical techniques. Pringle's maneuver was not usually performed during hepatic resection. The CUSA system (Valleylab, Boulder, CO) was used to transect the hepatic parenchyma. After hepatic resection had been completed, a disposable cholangiography catheter was inserted into the cystic duct and ligated in place. In both groups, 10 ml of dilute ICG solution (2.5 mg/ml; Dianogreen; Daiichi Sankyo Co., Tokyo) was injected into the bile duct, while the common bile duct was occluded temporarily distal to the cystic duct. Any sites of major leakage of dye from the cut surface of the remnant liver were repaired with z-sutures of 6-0 nonabsorbable suture material or by ligation with absorbable sutures, after which the absence of further leakage was confirmed by injecting 5–7 ml of saline. Only 1 injection of ICG solution was given in both groups. In the control group, the bile leakage test was completed after these procedures. The PDE group underwent fluorescent imaging with a PDE imaging system (Hamamatsu Photonics K.K.: Hamamatsu, Japan) after the first test of bile leakage with ICG solution. This procedure used a control unit (322×283×55 mm; 2.8 kg) and a camera unit (80×181×80 mm; 0.5 kg). The camera unit contained a charge-coupled device camera that filtered out light with a wavelength of less than 820 nm, as well as 36 light-emitting diodes with a wavelength of 760 nm.

The camera head was positioned 20 cm above the remnant liver, and the operating lights were turned off (the room lights were left on). This meant that the operating field was still visible to the surgeons and on the television monitor. Then fluorescent images of the cut surface of the liver were displayed on the monitor. These fluorescent images revealed 'white spots' at some sites on the liver surface, which represented potential bile leaks. The sites where the fluorescent images showed white spots were compressed with gauze, and then leakage was tested by injecting an additional 3–5 ml of saline (Fig 1). If fluorescence was detected through the gauze, it was assumed that these white spots indicated minor leaks on the cut surface of the liver and the presumably "leaking" bile ducts were repaired with sutures or by ligation.

The primary endpoint was the incidence of postoperative bile leakage, which was diagnosed by the following findings: detection of bile from the wound or the drain (total bilirubin in the drain fluid >3 times the serum level), intra-abdominal accumulation of bile confirmed by drainage, or demonstration of bile leakage on postoperative cholangiography. The secondary end-point was the incidence of postoperative morbidity. Postoperative complications were defined and classified by the modified Clavien system.[31] Briefly, grade I was any deviation from the normal postoperative course that did not require special treatment, while 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 1 (IVa) or multiple (IVb) major organs, and Grade V was death.

Statistical analysis. To validate the hypothesis that fluorescent imaging with ICG could decrease the rate of postoperative bile leakage from 20% to zero with an error of 0.05 and a error of 0.20, it was calculated that a sample size of 42 patients per group was required. Allowing for a dropout rate of 10% after randomization, it was concluded that at least 47 patients were needed in each group. Results are expressed as the 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, while the chi-square test or Fisher exact test was used for categorical data. The level of significance was set at $P < .050$. All statistical analyses were performed with SPSS for Windows 11.0J (SPSS, Chicago, IL).

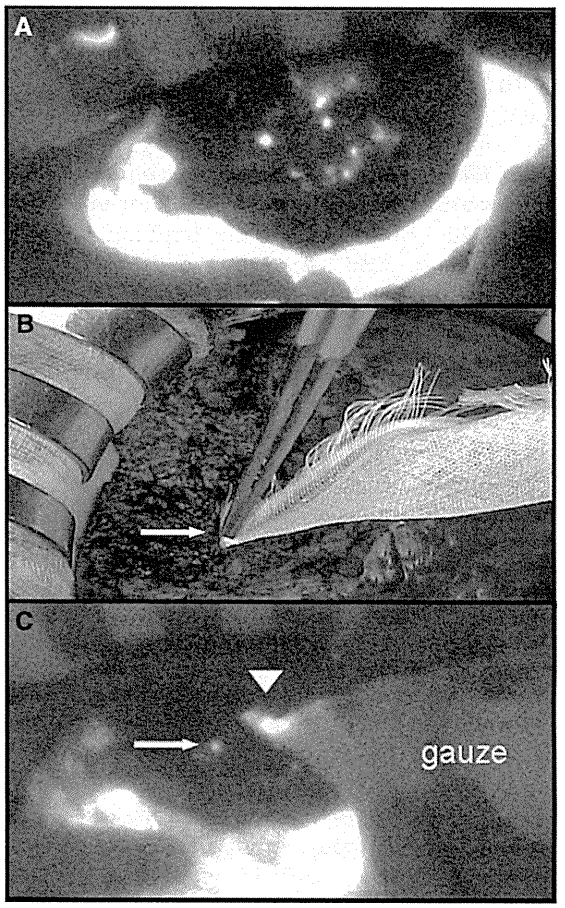

Fig 1. Fluorescent images obtained with the PDE system. (*A*) White spots (possible bile leakages) on the cut surface of the liver. (*B*) Minor leak (leaking duct), which is not visible to the surgeons (*arrow*), is compressed with gauze. (*C*) Fluorescent imaging after application of gauze reveals minor leakage on the cut surface of the liver (*arrow*), because fluorescence is detected through the gauze (*arrowhead*).

RESULTS

Among 109 eligible patients, seven were excluded, four refused to participate, and three underwent only exploratory laparotomy. Of the remaining 102 patients, 50 and 52 were randomized to the control group and the PDE group, respectively (Fig 2). Fifteen of 50 patients in the control group (30%) and 15 of 52 in the PDE group (29%) showed major leakage of ICG, which was detected as "leakage of green dye" without fluorescent imaging. In the control and PDE groups, repair was done with z-sutures of 6-0 non-absorbable or 4-0 absorbable suture material; all were repaired successfully during operation in both groups. PDE group was further detected with fluorescent imaging.

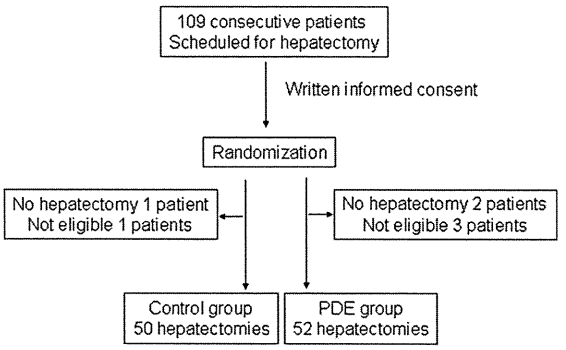

Fig 2. Flow chart of patient disposition. Among 109 eligible patients, 7 were excluded, 4 refused to participate, and 3 only underwent exploratory laparotomy. Of the remaining 102 patients, 50 and 52 were randomized to the control group and the PDE group, respectively. *PDE,* Photodynamic eye.

Patterns of fluorescence in the PDE group. In 10 of the 52 patients (19%) who underwent ICG fluorescent cholangiography after hepatic resection, no fluorescence was detected on the cut surface of the remnant liver, suggesting the absence of bile duct leaks at the operative margin. In the remaining 42 patients, the pattern of fluorescence was classified into the following 3 types: intact bile duct type (fluorescence revealed at 1 or more intact bile ducts on the cut surface of the liver, $n = 10$ [Fig 3]); injured bile duct type (leakage of dye from 1 or more bile duct stumps on the cut surface, $n = 25$ [Fig 4]); and unconfirmed type (there was leakage of ICG on the cut surface, but its source was unclear, $n = 7$, [Fig 5]). In the latter, these minor dye leaks were not able to be visualized by the surgeon and could only be detected by viewing fluorescent images on the monitor.

We did not treat the 10 patients with the intact duct pattern. In the 25 patients with injured bile ducts fluorescence detected, repair was done by z-suturing with 6-0 nonabsorbable suture material for 18 patients (1.5 ± 1.2 (mean ± SD) sutures per patient) and by ligation with 4-0 absorbable suture for the other 7 patients (1.1 ± 0.4 ligatures per patient). In the 7 patients with the unconfirmed type of ICG leakage, a sheet of fibrin sealant (TachoComb) was applied to the region of fluorescence (1.6 ± 0.8 pieces of sealant per patient; each piece measured 2.0 cm × 1.5 cm).

Preoperative characteristics, perioperative parameters, and pathologic findings. Table I summarizes the preoperative characteristics of the control and PDE groups. There were no differences between the 2 groups with respect to sex, age, hepatitis virus infection, liver function, and indications

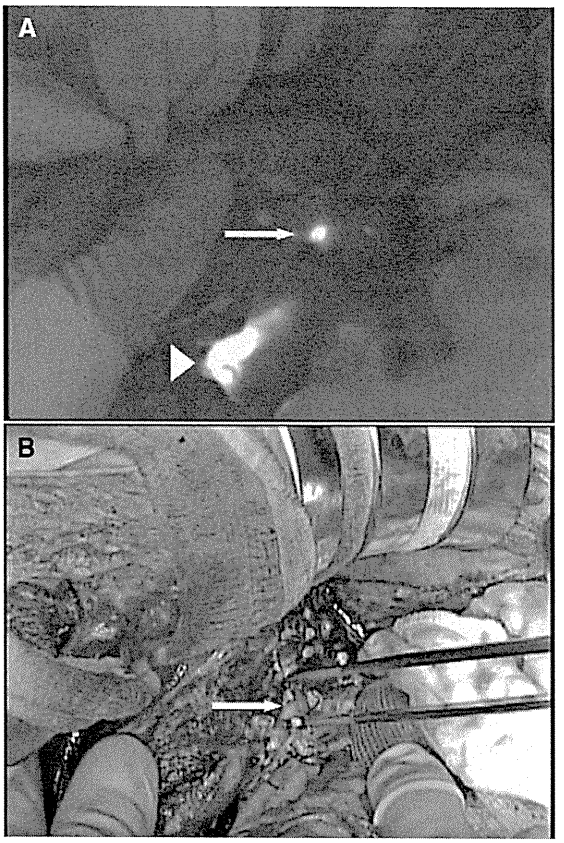

Fig 3. Intact bile duct type. (*A*) Fluorescent imaging identified one fluorescing duct on the cut surface of the liver (*arrow*). *Arrowhead,* common bile duct. (*B*) An intact bile duct corresponds to the fluorescing lesion on the cut surface (*arrow*).

for hepatic resection. As shown in Table II, the operative procedures, operating time, blood loss, blood transfusion, and hospital death rate also did not differ significantly between the 2 groups; however, the postoperative hospital stay of the PDE group was significantly less than that of the control group. The pathologic findings obtained in the 2 groups are also listed in Table II. There were no differences between the groups with respect to tumor size, number of tumors, and associated liver diseases.

The control group had a significantly greater rate of postoperative complications than the PDE group (8/50 [16%] vs 2/52 [4%], $P = .039$). In the control group, postoperative bile leakage occurred in 5 of 50 patients (10%), wound infection occurred in 3 patients (6%), and intractable ascites occurred in 2 patients (4%). In the PDE group, there was no postoperative bile leakage or bleeding. Postoperative wound infection occurred in 1 of 52 patients (2%) and intractable ascites or

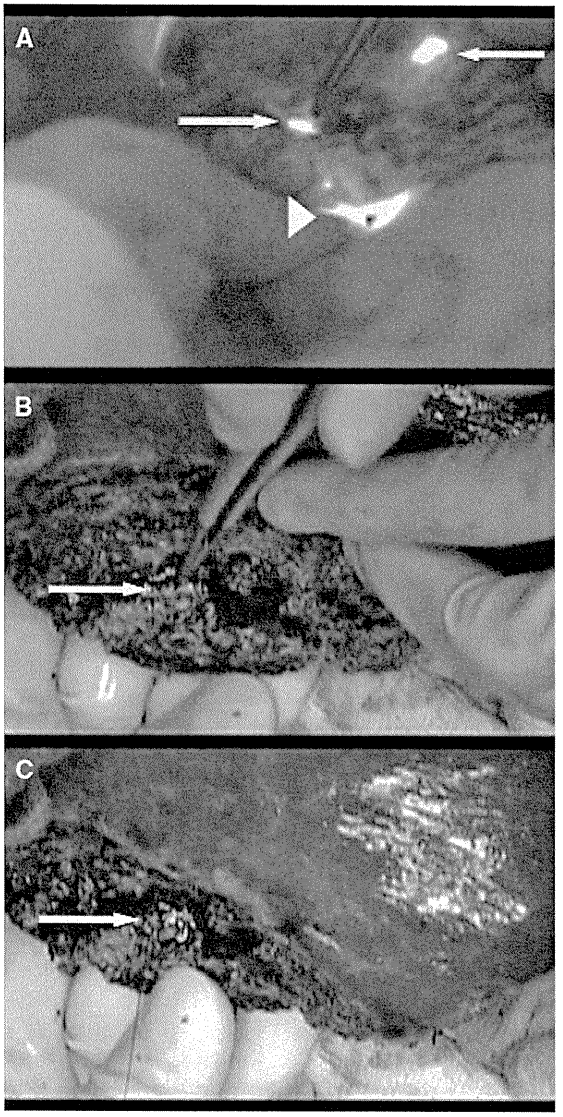

Fig 4. Injured bile duct type. (*A*) Fluorescent imaging identified 2 fluorescing ducts on the cut surface of the liver (*arrows*). The upper bile duct is intact (upper arrow). *Arrowhead*, common bile duct. (*B*) The lower fluorescing lesion corresponds to a partly closed bile duct stump (arrow). (*C*) The bile duct stump was repaired by z-sutures using 6-0 nonabsorbable thread (*arrow*).

pleural effusion occurred in 2 patients (4%). The rate of biliary complications showed a difference between the control and PDE groups ($P = .019$), whereas the rates of postoperative wound infection and intractable ascites or pleural effusion were similar for the 2 groups. In the control group, 4, 2, and 2 patients were Clavien grades II, IIIa, and IVa, respectively, while 1 patient each was grades II and IIIa in the PDE group.

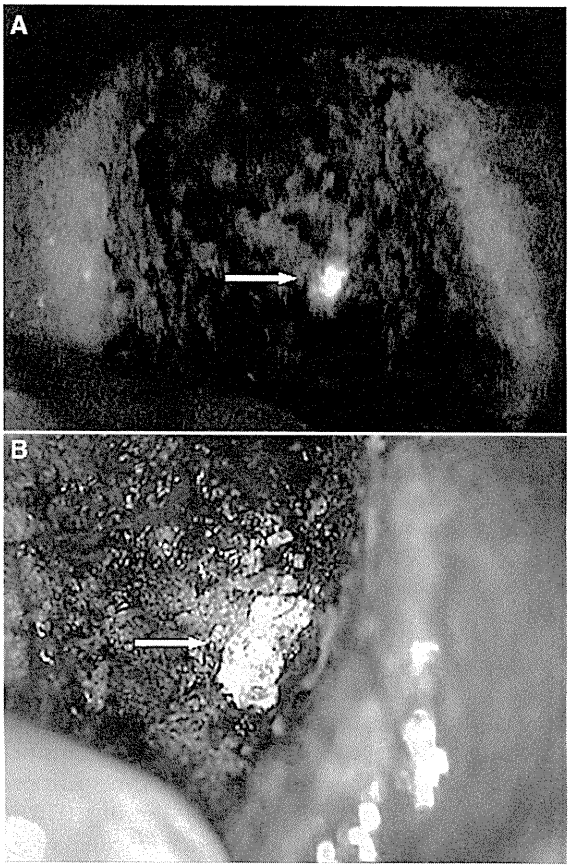

Fig 5. Unconfirmed bile type. (*A*) Fluorescent imaging identified a fluorescing area on the cut surface of the liver (*arrow*). (*B*) Fibrin sealant was applied to the fluorescent area (*arrow*).

In the present study, 5 of 102 hepatectomy patients (5%) had postoperative bile leakage that persisted for a median period of 8 weeks (range, 4-17). The operative procedures associated with postoperative bile leakage were extended hemihepatectomy in 1 patient, and hemihepatectomy and limited resection in two each. Percutaneous drainage of an abdominal abscess due to bile leakage was required in 2 patients, while percutaneous drainage of an abdominal abscess plus endoscopic naso-biliary drainage were needed in 1 patient. Leaks resolved spontaneously in the other 2 patients. In the 3 patients with percutaneous or nasal drainage, the injured bile ducts showed communication with the main biliary tree.

Laboratory parameters. The laboratory parameters investigated were the white blood cell count (WBC) and the serum C-reactive protein (CRP) level. WBC ($\bar{x} \pm SD$) did not differ between the 2 groups from postoperative day 1 to day 7, ranging

Table I. Preoperative clinical characteristics of the 2 groups

	Control group (n = *50*)	*PDE group* (n = *52*)	P *value*
Sex (male:female)	37:13	39:13	.908†
Age (years)*	68.2 (11.0)	70.4 (5.5)	.339‡
HBV: HCV: nonBC	13:19:18	10:24:18	.627†
ICGR15 (%)*	11.8 (5.7)	15.3 (7.6)	.062‡
Platelet count ($\times 10^4/\mu l$)*	19.3 (9.5)	17.3 (8.0)	.403‡
Total bilirubin (mg/dl)*	0.72 (0.26)	0.79 (0.23)	.291‡
Albumin (g/dl)*	3.84 (0.49)	3.88 (0.45)	.777‡
Prothrombin time (%)*	97 (11)	92 (12)	.105‡
AST (IU/L)*	36 (21)	41 (29)	.476‡
Child-Pugh class A:B	48:2	49:3	.679†
Diagnosis			
Hepatocellular carcinoma	34 (68)	37 (71)	.936†
Metastatic liver tumor	12 (24)	12 (23)	
Intrahepatic cholangiocarcinoma	2 (4)	1 (2)	
Benign disease	2 (4)	2 (4)	

*Values are mean (SD).
†χ^2 test.
‡*t* test.
Values in parentheses are percentages unless otherwise indicated.
PDE, Photodynamic eye; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *NBC,* nonhepatitis B or C virus; *ICGR15,* indocyanine green retention rate at 15 min; *AST,* aspartate aminotransferase.

Table II. Intraoperative and postoperative characteristics

	Control group (n = *50*)	*PDE group* (n = *52*)	P *value*
Operative procedure			
Extended hemihepatectomy	5 (10)	6 (12)	.749†
Hemihepatectomy	15 (30)	11 (21)	
Sectionectomy	12 (24)	14 (27)	
Segmentectomy	0 (0)	1 (2)	
Limited resection	18 (36)	20 (38)	
Operating time (min)*	337 (126)	328 (124)	.805‡
Operative blood loss (ml)*	992 (1504)	886 (1402)	.592‡
Perioperative blood transfusion	13 (26)	10 (19)	.414†
Operative mortality	0 (0)	0 (0)	1.000†
Postoperative hospital stay (days)*	18.2 (15.9)	10.4 (3.8)	.023‡
Tumor size (cm)*	5.0 (4.6)	5.3 (4.9)	.976‡
Number of tumors			
Single	37 (74)	43 (83)	.286†
Multiple	13 (26)	9 (17)	
Associated liver disease			
Normal	17 (34)	15 (29)	.534†
Fibrosis or hepatitis	19 (38)	17 (33)	
Cirrhosis	14 (28)	20 (38)	

*Values are the mean (SD).
†χ^2 test.
‡*t* test.
Values in parentheses are percentages unless otherwise indicated.

from 9800 ± 2700 cells/cm^2 to 6500 ± 1700 cells/cm^2. In contrast, serum CRP was significantly less in the PDE group on postoperative days 5 and 7. The respective values were 3.6 ± 2.1 vs 5.9 ± 5.2 (P = .044) on day 5, and 2.5 ± 1.7 vs 5.2 ± 4.6 (P = .005) on day 7.

DISCUSSION

Postoperative bile leakage remains a challenging problem in patients undergoing liver resection, especially after major hepatectomy, and can be associated with serious complications such as sepsis and liver failure.[7] The object of a bile leak

test is to detect inadequately closed bile duct stumps on the cut surface of the liver. Intraoperative bile leak tests cannot completely exclude the possibility of postoperative bile leakage, because leakage can occur from small, segregated ducts that are not in communication with the main biliary tree.[32] The ability of several intraoperative measures for visualizing and preventing postoperative bile leaks has been reported, including detection of leaks by injection of saline,[9] methylene blue,[5,15] or ICG,[6,14] the "white test",[18,19] or intraoperative cholangiography,[17] as well as use of an ultrasonic dissector,[5] spreading fibrin glue on the cut surface of the liver,[33] and common bile duct drainage using a T-tube or a thin catheter inserted via the cystic duct stump.[34] Nevertheless, there is no standard method for the prevention of postoperative bile leakage. We suspected that small bile duct stumps on the cut surface of the liver might be missed by the usual bile leak tests.

The advantages of ICG fluorescent cholangiography are its safety and feasibility. ICG is already used worldwide to evaluate liver function before operation and the incidence of adverse reactions after intravenous injection of ICG is very low (approximately 0.003%).[35] The major limitation of ICG fluorescent cholangiography is that it is impossible to visualize deep intrahepatic bile ducts or extrahepatic bile ducts covered by surrounding organs with this technique because of the limited tissue penetration of the near-infrared light emitted by the current imaging system. The present study, however, showed that this imaging method made it possible to evaluate details on the cut surface of the liver. Five patients developed postoperative bile leakage among the 50 patients in the control group versus no bile leakage among the 52 patients in the PDE group. During the operation, 25 of 52 patients in the PDE group were found to have inadequate closure of bile duct stumps on the cut surface of the liver which could be detected by fluorescent imaging, and these stumps were subsequently treated by suture or ligation.

In conclusion, ICG fluorescent cholangiography has the ability to detect leaking bile duct stumps missed by a conventional bile leak test. ICG fluorescent cholangiography can be a useful application for the prevention of bile leakage after hepatic resection.

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