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Bile Leakage After Hepatectomy for Liver Tumors

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This study aimed to clarify the predictive factors for bile leakage after hepatectomy for liver tumor in terms of the International Study Group of Liver Surgery (ISGLS) definition. Between August 2006 and July 2012, 242 patients with a diagnosis of liver tumor underwent hepatectomy in our department, and the total bilirubin level of peritoneal drainage fluid prior to removal of the abdominal drains was examined. The data on all of the patients were analyzed retrospectively to identify the factors that might significantly affect the postoperative bile leakage. There was no grade C bile leakage, and grade A was documented in 65 patients (26.9%) and grade B in 7 patients (2.9%) in terms of the ISGLS definition. Although there was no significant difference in postoperative hospital stay between grade A bile leakage only and those without bile leakage ($P = 0.933$), a significant difference was noted between grades A and B (median, 11.0 versus 21.0 days; $P < 0.001$). Multivariate analysis revealed 4 independent significant predictive factors: prolonged operation time ($P = 0.040$), cholecystectomy ($P = 0.048$), non–portal vein embolization ($P = 0.010$), and preoperative chemotherapy ($P = 0.021$). The ISGLS definition of bile leakage is clinically useful. Prolonged operation time, cholecystectomy, non–portal vein embolization, and preoperative chemotherapy were significant independent risk factors of bile leakage in this study.

Key words: Bile leakage – Hepatectomy – Liver tumor – International Study Group of Liver Surgery (ISGLS)

Hepatic resection has been established as the treatment of choice for liver tumors in terms of the increasing safety of the procedure.[1–3] The indications for hepatectomy are now expanding, especially for colorectal liver metastasis as a multidisciplinary strategy because of the recent efficacy of aggressive perioperative systemic chemotherapy,[4–8] and the prevalence of preoperative portal vein embolization (PVE) providing the compensatory hypertrophy of the future remnant liver.[9,10] Howev-

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er, the morbidity after hepatectomy for liver tumors remains high in comparison with that of surgery for gastrointestinal malignancies. Bleeding and liver failure are known to be serious morbidities after hepatectomy, and the bile leakage from the raw surface of the liver is one of the significant complications affecting the postoperative hospital stay. Bile leakage is expressed in several terms, such as bile leak, biliary fistula, biliary leakage, and biliary leak. Because the definition of bile leakage after hepatectomy was not standardized,[11] several authors have reported varying results ranging from 3.6% to 33% of its incidence.[12–14] The grading system for bile leakage also was not established. A definition and grading of severity of bile leakage after hepatobiliary and pancreatic surgery have been proposed by the International Study Group of Liver Surgery (ISGLS),[15] similar to that for pancreatic fistula after pancreatic resection, attempting to standardize evaluation of clinical studies.[16,17] Although bile leakage potentially causes bile peritonitis and/or sepsis with fatal results, some bile leakage does not affect clinical outcome according to ISGLS grading. The aims of this study were to clarify the incidence of bile leakage in terms of the ISGLS definition and to identify the predictive factors for the bile leakage after hepatectomy for liver tumor in our department.

Patients and Methods

Patients

Between August 2006 and December 2012, a total of 325 patients with tentative diagnoses of liver tumors underwent hepatectomy in Aichi Cancer Center Hospital.

Sixteen patients who underwent bilioenteric anastomosis and a patient who developed bile duct injury necessitating biliary drainage were excluded. Total bilirubin level of peritoneal drainage was not measured in 66 patients. Accordingly, 242 patients whose total bilirubin level of peritoneal drainage fluid was examined prior to removal of abdominal drains were analyzed in this study.

Surgery

Liver transection was performed at the preference of the operating surgeon using an ultrasonic device [cavitron ultrasonic surgical aspirator (CUSA)] or forceps clamp crushing method. The hepatic pedicle occlusion (Pringle maneuver) was performed during both hepatic artery and portal vein clamping for 20 minutes at 5-minute intervals. Simultaneous cholecystectomy was performed if necessary, and the bile leak test was carried out after liver transection in terms of air injection into biliary tree by inserting a 4 Fr catheter via cystic duct. If air leakage was identified from a raw surface of the liver or the exposed Glissonian capsule, meticulous suture closure was performed. We do not routinely apply fibrin sealants or collagen fleece to the raw surface of the liver. Prophylactic drain was placed along the raw surface of the liver, and the number of drainage tubes was determined according to the number of liver resection sites.

Perioperative management

Preoperative laboratory data, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, serum total bilirubin, C-reactive protein, serum total protein level, serum albumin level, white blood cell count, hemoglobin level, platelet count, and prothrombin time, were investigated.

We principally examined the total bilirubin concentration of the drainage fluid prior to drain withdrawal. When the bilirubin concentration of the drainage fluid was lower than 5.0 mg/dL or increased 2-fold over the serum level in patients with hyperbilirubinemia greater than 2.5 mg/dL, we removed the prophylactic drain around the fifth postoperative day. The therapeutic drain for management of bile leakage was also removed when the total bilirubin concentration of the drainage fluid met our institutional criteria in this study period.

Definition of bile leakage

In this study, we reviewed the bile leakage according to the ISGLS definition and grading (Table 1), not our previous institutional criteria. Bile leakage is defined as fluid with an increased bilirubin concentration in the abdominal drain after postoperative day 3, or as the need for radiologic intervention. It was not considered as bile leakage when a high bilirubin concentration of drainage fluid at postoperative day 1 subsided at postoperative day 3, in line with the ISGLS definition.

Statistical analysis

Patients were dichotomized into groups with none, and grade A or above. Differences in the nominal or ordinal variables between the 2 groups were

Table 1 Definition and grading of bile leakage after hepatobiliary and pancreatic surgery proposed by the ISGLS[15]

Definition	Bile leakage is defined as fluid with an increased bilirubin concentration in the abdominal drain or in the intra-abdominal fluid on or after postoperative day 3, or as the need for radiologic intervention (*i.e.*, interventional drainage) because of biliary collections or relaparotomy resulting from bile peritonitis. Increased bilirubin concentration in the drain or intra-abdominal fluid is defined as a bilirubin concentration at least 3 times greater than the serum bilirubin concentration measured at the same time.
Grade	
A	Bile leakage requiring no or little change in patients' clinical management
B	Bile leakage requiring a change in patients' clinical management (*e.g.*, additional diagnostic or interventional procedures) but manageable without relaparotomy, or a grade A bile leakage lasting for >1 wk
C	Bile leakage requiring relaparotomy

examined using Fisher exact test. Differences in quantitative variables between the 2 groups were evaluated using the Mann-Whitney *U* test. Predictive factors for the 2 groups were evaluated using binomial logistic regression analysis with backward selection. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, North Carolina). A *P* value of <0.05 was considered statistically significant. All analyses in this study were supervised by a statistician.

Results

Data from 242 patients were analyzed. There were 79 women (32.6%) and 163 men (67.4%), with a median age of 65 years (range, 33–87 years). There were 103 patients with primary liver tumor (42.6%), including hepatocellular carcinoma for 90, intrahepatic cholangiocarcinoma for 7, and other primary or benign tumor for 6; and 139 patients with metastatic tumor (57.4%), including colorectal liver metastasis for 125 and other liver metastasis for 14. The hepatitis B surface antigen was positive in 33 patients (13.7%), and the hepatitis C antibody was positive in 31 patients (12.8%). The median body mass index was 22.5 (range, 16.2–34.2). A total of 53 patients (21.9%) had diabetes mellitus. The median indocyanine green retention rate at 15 minutes (ICGR15) was 8.6% (range, 1.0–34.7%). A total of 31 patients (12.8%) underwent preoperative PVE prior to hepatectomy. There were 164 patients (68.3%) who had undergone previous abdominal surgery, and 42 patients (17.4%) underwent repeat hepatectomy. There were 89 patients (37.1%) who underwent preoperative chemotherapy. Various type of chemotherapy—such as FOLFOX (5-fluorouracil/leucovorin plus oxaliplatin), and/or FOLFILI (5-fluorouracil/leucovorin plus irinotecan), and XELOX (capecitabine plus oxaliplatin)—with or without molecular targeting agent prior to hepatectomy were performed in 40 patients (44.9%), including 5 who underwent hepatic arterial infusion chemotherapy and 9 with hepatic arterial chemoembolization.

The number of resected tumors was single in 147 patients (60.7%) and plural (range, 2–11) in 95 patients (37.5%). The number of resection sites was single in 185 patients (76.4%), and plural (range, 2–8) in 57 patients (23.6%). The median maximum size of tumor was 3.2 cm in diameter (range, 0.3–23 cm). Only anatomic liver resection was carried out in 110 patients (45.5%), combined anatomic and nonanatomic partial liver resection was carried out in 32 patients (13.2%), and only nonanatomic partial resection was applied in 100 patients (41.3%), respectively. Thoracotomy was performed in 52 patients (21.9%).

Liver transection was performed at the preference of the operating surgeon using the CUSA in 152 patients (62.8%), and forceps clamp crushing method in 90 patients (37.2%). The hepatic pedicle occlusion was performed in 224 patients (92.6%), and median occlusion time was 60 minutes (range, 5–182 minutes). Simultaneous cholecystectomy was performed in 141 patients (69.1%), and bile leak test was carried out in 71 patients (29.7%). The median weight of resected liver was 215 g (range, 10–2500 g). Additional surgical procedures, such as simultaneous gastrointestinal resection, were applied for 24

Table 2 Clinical outcome according to bile leakage

Bile leakage	Postoperative hospital stay, d, median (minimum–maximum)	*P*
None (n = 170)	11 (6–62)	
Grade A (n = 65)	11 (8–21)	0.933 (versus no bile leakage)
Grade B (n = 7)	21 (14–25)	<0.001 (versus grade A bile leakage)

Table 3 Possible clinical and perioperative risk factors for bile leakage (univariate analysis)

Factors	Median (range)	Bile leakage, No. of patients			*P*
		Absent	Present	Total	
Overall		170	72	242	
Age, y	65 (33–87)				
≤65 y		83	42	125	
>65 y		87	30	117	0.206
Sex					
Male		117	46	163	
Female		53	26	79	0.458
Disease					
Primary		75	28	103	
Metastasis		95	44	139	0.48
HBsAg					
Positive		25	8	33	
Negative		144	64	208	0.542
HCV Ab					
Positive		24	7	31	
Negative		146	65	211	0.406
Body mass index, kg/m^2	22.5 (16.2–34.2)				
≤22.5 kg/m^2		85	38	123	
>22.5 kg/m^2		83	34	117	0.78
ICG R15, %	8.6 (1.4–25.6)				
≤8.6%		80	40	120	
>8.6%		87	32	119	0.324
DM					
Present		41	12	53	
Absent		129	60	189	0.236
PVE					
Performed		27	4	31	
Not performed		143	68	211	0.034
Chemotherapy prior to hepatectomy					
Performed		56	33	89	
Not performed		113	38	151	0.058
Previous abdominal surgery					
Present		115	49	164	
Absent		54	22	76	1.000
Repeat hepatectomy					
Yes		30	12	42	
No		139	60	199	1.000

patients (11.4%). The median operation time was 217 minutes (range, 70–595 minutes); the median intraoperative blood loss was 378 g (range, 0–5500 g). The in-hospital mortality rate was zero, and morbidity of Clavien-Dindo grade III or more was observed in 16 patients (6.6%).

Although there was no grade C bile leakage, grade A bile leakage was documented in 65 patients (26.9%) and grade B bile leakage in 7 patients (2.9%). Accordingly, the bile leakage was detectable in 72 patients, and the incidence of bile leakage in terms of the ISGLS definition was 29.8% in the present study. No patients with grade A bile leakage required further intervention to control bile leakage after withdrawal of the abdominal drain. The overall median length of postoperative hospital stay was 11 days (range, 6–62 days) in all. There were no significant differences in postoperative hospital stay (median, 11.0 versus 11.0 days) between patients with grade A bile leakage and those without bile leakage. The median postoperative hospital stay in patients with grade B bile leakage was 21.0 (range, 14–25 days). This figure was significantly longer in comparison with that for patients with grade A bile leakage ($P < 0.001$; Table 2).

Univariate analyses

Clinical and perioperative variables

The 27 clinical and perioperative variables are shown in Table 3. Operation time of longer than

Table 3 Continued

Factors	Median (range)	Bile leakage, No. of patients			*P*
		Absent	Present	Total	
Number of tumors					
Single		103	44	147	
Multiple		67	28	95	1.000
Maximum diameter, cm	3.2 (0.3–23.0)				
≤3.2 cm		84	38	122	
>3.2 cm		85	34	119	0.676
Number of resection sites					
Single		129	56	185	
Multiple		41	16	57	0.869
Anatomic hepatectomy or partial hepatectomy					
Anatomic		98	44	142	
Partial		72	28	100	0.670
Operation time, min	217 (70–595)				
≤217 min		93	30	123	
>217 min		77	42	119	0.069
Intraoperative blood loss, g	378 (0–5500)				
≤378 g		89	32	121	
>378 g		81	40	121	0.325
Thoracotomy					
With		33	19	52	
Without		133	52	185	0.304
Liver transection device					
CUSA		101	51	152	
Pean forceps		69	21	90	0.110
Pedicle occlusion time, min	60 (5–182)				
≤60 min		94	34	128	
>60 min		66	30	96	0.458
Cholecystectomy					
Performed		98	43	141	
Not performed		51	12	63	0.124
Bile leak test					
Performed		48	23	71	
Not performed		120	48	168	0.642
Additional surgical procedure					
Performed		14	10	24	
Not performed		156	62	218	0.238
Red blood cell transfusion					
Performed		10	3	13	
Not performed		159	69	228	0.760
Fresh frozen plasma transfusion					
Performed		14	4	18	
Not performed		154	68	222	0.597
Weight of resected liver, g	215 (10–2500)				
≤215 g		83	34	117	
>215 g		80	36	116	0.776

Ab, antibody; DM, diabetes mellitus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ICG R15, indocyanine green retention value at 15 minutes.

217 minutes ($P = 0.069$), ultrasonic device ($P = 0.110$), cholecystectomy ($P = 0.124$), non-PVE ($P = 0.034$), and preoperative chemotherapy ($P = 0.058$) were regarded as possible predictive factors ($P < 0.2$) affecting postoperative bile leakage on univariate analysis. For 22 other variables, there were no significant differences between patients with and without bile leakage.

Preoperative laboratory data

The 12 items for preoperative laboratory data are shown in Table 4. Aspartate aminotransferase

Table 4 Possible preoperative laboratory data as risk factors for bile leakage (univariate analysis)

Preoperative factors	Median (range)	Grade B bile leakage, No. of patients			*P*
		Absent	Present	Total	
AST, IU/L	25 (12–164)				
≤25 IU/L		79	45	124	
>25 IU/L		91	27	118	0.025
ALT, IU/L	21 (3–173)				
≤21 IU/L		83	40	123	
>21 IU/L		87	32	119	0.399
ALP, IU/L	267 (46–1062)				
≤267 IU/L		87	34	121	
>267 IU/L		83	37	120	0.673
γ-GTP, IU/L	46 (10–476)				
≤46 IU/L		78	36	114	
>46 IU/L		78	32	110	0.772
T-Bil, mg/dL	0.7 (0.3–2.1)				
≤0.7 mg/dL		103	56	159	
>0.7 mg/dL		67	16	83	0.012
CRP, mg/dL	0.10 (0.01–14.19)				
≤0.10 mg/dL		74	27	101	
>0.10 mg/dL		66	30	96	0.531
Total protein, g/dL	7.1 (5.5–9.0)				
≤7.1 g/dL		95	35	130	
>7.1 g/dL		74	36	110	0.395
Albumin, g/dL	4.1 (1.9–4.7)				
≤4.1 g/dL		96	41	137	
>4.1 g/dL		73	31	104	1.000
WBC, per μL	5025 (2230–19,750)				
≤5025/μL		86	35	121	
>5025/μL		84	37	121	0.888
Hemoglobin, g/dL	13.0 (8.6–16.5)				
≤13.0 g/dL		87	39	126	
>13.0 g/dL		83	33	116	0.676
Platelets, $\times 10^4/\mu L$	19.3 (6.6–54.2)				
$\leq 19.3 \times 10^4/\mu L$		93	29	122	
$> 19.3 \times 10^4/\mu L$		77	43	120	0.049
Prothrombin time, %	87 (52–122)				
≤87%		91	29	120	
>87%		73	42	115	0.047

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; γ-GTP, γ-glutamyl transpeptidase; T-Bil, serum total bilirubin; TP, serum total protein level; WBC, white blood cell count.

greater than 25 U/L ($P = 0.025$), serum total bilirubin level of 0.7 mg/dL or lower ($P = 0.012$), platelet level greater than $19.3 \times 10^4/\mu L$ ($P = 0.049$), and prothrombin time greater than 87% ($P = 0.047$) were regarded as possible predictive factors ($P < 0.2$) affecting postoperative bile leakage on univariate analysis. The other 8 preoperative variables showed no significant differences between patients with and without bile leakage.

Multivariate analysis

Multivariate analysis selected 9 variables showing a definitive or marginal significance ($P < 0.2$); using a logistic regression analysis with backward selection identified 4 independent predictive factors for postoperative bile leakage: operation time longer than 217 minutes, ($P = 0.040$; odds ratio, 2.161), cholecystectomy ($P = 0.048$; odds ratio, 2.194), non-PVE ($P = 0.010$; odds ratio, 0.205), and preoperative chemotherapy ($P = 0.021$; odds ratio, 2.326; Table 5).

Discussion

Despite the recent advances in hepatobiliary surgical techniques,[18] bile leakage still shows significant postoperative morbidity affecting surgical outcomes,[19–22] and occasionally causing such life-threatening situations as bile peritonitis or sepsis.[23] Thus, the hepatobiliary surgeon must pay due

Table 5 Risk factors associated with bile leakage after hepatectomy for liver tumors

Variable	Odds ratio	95% Confidence interval		*P*
Operation time >217 min	2.161	1.034	4.513	0.040
Cholecystectomy	2.194	1.007	4.778	0.048
PVE	0.205	0.062	0.680	0.010
Preoperative chemotherapy	2.326	1.136	4.765	0.021

attention to this morbidity and its treatment strategy. Although various risk factors relating to posthepatectomy bile leakage have been reported,[24–26] the definitions of bile leakage have varied. The ISGLS has proposed a consensus definition based on the postoperative course of bilirubin concentrations in serum and drainage fluid.

Using a uniform definition for bile leakage is indispensable for enabling standardized comparison of the results of different clinical reports. In the present study, we have validated whether or not the grading of bile leakage proposed by the ISGLS is applicable to our cases.

According to ISGLS grading, grade A bile leakage requires little or no change in a patient's clinical course. In this study, there are no significant differences in hospital stay between patients with grade A bile leakage and those without bile leakage. On the other hand, there is a significant difference between grades A and B. The ISGLS definition and grading are clinically relevant and are useful for searching the risk factors of bile leakage in our hepatectomized patients.

We first sought to find risk factors of grade B bile leakage, because grade A bile leakage actually does not affect the clinical outcome according to the ISGLS in our series.

However, there were no independent predictive factors by multivariate analysis. The incidence of bile leakage ranged from 3.6% to 33.0% in the previous reports.[12–14] In our present study, the incidence of all bile leakage was 72 cases (29.8%), but grade B bile leakage comprised only 7 cases (2.9%). We consider that the slight grade B bile leakage is a potential reason for failing to detect significant independent predictive factors. Thus, we searched for predictive factors of not only grade B but all bile leakage. This is still crucial because grade A bile leakage has the potential to change into grade B bile leakage.

Several groups have reported that prolonged operation time was a risk factor for bile leakage.[24,27,28] In the present study, operation time longer than the median (217 minutes) was identified as an independent risk factor of bile leakage, similar to those in previous reports. Prolonged operation time might be the result of a technically difficult and complicated operation.[24]

Preoperative chemotherapy was one of the independent risk factors for bile leakage in this study. According to the EORTC40983 trial,[29] patients treated with perioperative chemotherapy (FOLFOX4) had more reversible postoperative complications (25%) than patients with surgery alone (16%; $P = 0.04$). The incidence of bile leakage in patients with perioperative chemotherapy was almost double compared with the group of surgery alone (8% versus 4%). Karoui *et al*[30] reported that preoperative chemotherapy was an independent risk factor for postoperative morbidity. They also mentioned that pathologic changes and sinusoidal dilatation with atrophy of hepatocytes and/or hepatocytic necrosis were significantly increased in the preoperative chemotherapy group. These parenchymal changes may influence healing or regeneration of the remnant liver. A multidisciplinary approach to colorectal liver metastasis will be more prevalent in the future. In such a situation, we must pay careful attention to adopting hepatectomy for patients with preoperative chemotherapy.

Multivariate analysis also revealed cholecystectomy as a predictive factor of bile leakage. The function of the gallbladder is to restore bile juice produced from hepatocytes. It is thought that removal of the gallbladder as a storage place will elevate the pressure in the bile duct, resulting in a higher incidence of bile leakage. Although bile leakage after cholecystectomy is rare (0.2%–1.5%),[31] it still occurs and results in a miserable postoperative course in some cases. Kimura *et al*[32] reported that bile leakage after cholecystectomy, though not common, is actually detectable in terms of routine drainage tube placement.

Non-PVE was also recognized as a predictive factor of bile leakage. The rates of PVE with or without bile leakage were 5.6% and 15.8%, respectively. This difference is statistically significant ($P = 0.010$). Right hemihepatectomy was performed in 27 of 31 PVE cases (87.1%). In these procedures, Glissonian sheath was cut down at the root of the hepatic duct and was never exposed on the raw surface of the resected liver. This feature may possibly have an influence on the incidence of bile leakage.

There was no in-hospital mortality, there was a 6.6% morbidity for grade IIIa or more severe

Clavian-Dindo classification, and there was no grade C bile leakage. These findings were also similar in 66 patients excluded from the present analysis (no mortality and no grade C bile leakage, and 7.5% morbidity for grade IIIa or more). It must therefore be reasonable to conclude that our strategy of hepatectomy for liver tumors is valid from the viewpoint of short-term outcome.

In conclusion, grade A bile leakage was actually clinically silent as defined by the ISGLS; therefore, the ISGLS classification may be considered useful in clinical practice and may contribute to standardized comparison of the results of various clinical outcomes of hepatic surgery. Prolonged operation time, cholecystectomy, non-PVE, and preoperative chemotherapy were significant independent risk factors of bile leakage in this study.

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