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ORIGINAL SCIENTIFIC REPORT

A Clear Difference Between the Outcomes After a Major Hepatectomy With and Without an Extrahepatic Bile Duct Resection

Takehiro Takagi[1] · Yukihiro Yokoyama[1] · Toshio Kokuryo[1] · Tomoki Ebata[1] · Masahiko Ando[2] · Masato Nagino[1]

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Abstract

Background The procedure of a simple hepatectomy and a hepatectomy with an extrahepatic bile duct resection and subsequent choledocho-jejunostomy is largely different. However, these two procedures are sometimes included in the same category. There are no studies comparing postoperative course and liver regeneration rate after a major hepatectomy with and without an extrahepatic bile duct resection.

Methods We retrospectively reviewed medical records of 245 patients who underwent a right hepatectomy (RH, $n = 55$) or RH with an extrahepatic bile duct resection (RHEBR, $n = 190$). Postoperative complications, including incidence of posthepatectomy liver failure (PHLF) and hepatic regeneration rates after surgery, were evaluated.

Results The incidence of PHLF was considerably higher in the RHEBR group than in the RH group (39.5 vs. 16.4 %, $p = 0.001$). The percentage of newly regenerated liver volume after the hepatectomies on postoperative days 6–8 was significantly lower in the RHEBR group than in the RH group (14.0 % in the RH; 7.9 % in the RHEBR group, $p < 0.001$). Especially type of surgery (RHEBR) was the only independent risk factor for an impaired liver regeneration rate by univariate and multivariate analyses. Furthermore, estimated hepatic regeneration rate by stepwise linear regression analysis in the RHEBR group was 7.1 % lower (95 % confidence interval 1.8–12.3, $p = 0.011$) than in the RH group.

Conclusion These results suggest that the procedure of extrahepatic bile duct resection has a possibility of adverse impact on the postoperative outcome after major hepatectomy.

✉ Yukihiro Yokoyama
yyoko@med.nagoya-u.ac.jp

Takehiro Takagi
takagi@med.nagoya-u.ac.jp

Toshio Kokuryo
kokuryoh@med.nagoya-u.ac.jp

Tomoki Ebata
tomoki@med.nagoya-u.ac.jp

Masahiko Ando
mando@med.nagoya-u.ac.jp

Masato Nagino
nagino@med.nagoya-u.ac.jp

[1] Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

[2] Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, Japan

Introduction

Surgical procedures for a perihilar cholangiocarcinoma often need to include a major hepatectomy with an extrahepatic bile duct resection and subsequent choledocho-jejunostomy. This procedure is largely different from the simple hepatectomy without extrahepatic bile duct resection in terms of operative invasiveness and the incidence of postoperative complications [1]. However, when analyzing the data of major hepatectomies, these two procedures are sometimes included in the same category of operative procedure. There are no previous reports comparing postoperative course after a major hepatectomy with and without an extrahepatic bile duct resection.

Recent study demonstrated that a choledocho-jejunostomy has an adverse impact on the process of early stage liver regeneration after a 70 % hepatectomy in a rat model [2]. In this basic study, the liver regeneration rate was significantly lower in rats that underwent a hepatectomy with a choledocho-jejunostomy than in rats that underwent a hepatectomy alone. Moreover, several clinical studies have reported that the presence of cholangitis after a major hepatic resection for biliary carcinoma has a major adverse impact on short-term postoperative outcomes [3–5]. Regurgitating cholangitis through a bilio-enteric anastomosis is a common complication after a choledocho-jejunostomy procedure.

The aim of this study was to compare clinical outcomes between two procedures; a right hepatectomy with and without an extrahepatic bile duct resection and subsequent choledocho-jejunostomy. Only patients with right hepatectomy were selected because percentage of liver resection volume was similar in two groups. Furthermore, to adjust the background, a propensity matching score was used when comparing liver regeneration rate between the two groups.

Patients and methods

Patients

This study included consecutive patients who underwent a major hepatectomy in the First Department of Surgery, Nagoya University Hospital in Nagoya, Japan. Written informed consent approved by the Nagoya University Hospital Human Research Review Committee was obtained from each patient before study enrollment.

Preoperative patient management

When patients had jaundice due to biliary obstruction, appropriate biliary drainage, either using endoscopic nasobiliary drainage, an endoscopic biliary stent, or percutaneous transhepatic biliary drainage, was performed. Indocyanine green test, including retention rate at 15 min (ICGR15) and plasma disappearance rate (ICGK), and computed tomography (CT) volumetric scans were routinely performed to evaluate the functional reserve of a future liver remnant [6]. A preoperative portal vein embolization (PVE) was performed when the extent of the liver resection exceeded 60 % and/or functional reserve of a future liver remnant was considered insufficient [7].

Surgery

Liver resections were conducted using intermittent clamping of both the portal vein and hepatic artery (clamping for 15 or 20 min at 5-min intervals). In the RHEBR group, a choledocho-jejunostomy was performed using a Roux-en-Y anastomosis as previously reported [8, 9]. All anastomosed bile ducts were stented and externally drained with a 6-Fr polyvinyl chloride tube (PTBD tube; Hakko, Chikuma, Japan) through the jejunal stump used for the choledocho-jejunostomy (transjejunal route). Therefore, no case showed a severe dilatation of a biliary tree due to anastomotic stenosis, which was confirmed by routinely performed postoperative CT scans.

Recording clinical data and postoperative complications

Several factors were measured during the preoperative, intraoperative, and postoperative periods. Levels of white blood cell (WBC) counts, serum C-reactive protein (CRP), total bilirubin (T-bil), and prothrombin time-international normalized ratio (PT-INR) were analyzed on postoperative days 5 and 7. PHLF and posthepatectomy bile leakage were defined according to the criteria of the International Study Group of Liver Surgery (ISGLS) definition [10–12]. Postoperative infectious complications, including wound infection, cholangitis, intra-abdominal abscess, liver abscess, and bacteremia detected by a culture method, were also recorded for up to 30 days after the procedure. A diagnosis of cholangitis should fulfill the following criteria: a sustained fever requiring treatment with antibiotics, increased serum hepatobiliary enzymes, and isolation of bacteria from bile cultures with no focused infections other than cholangitis [5].

Calculation of postoperative hepatic regeneration

A postoperative CT scan was performed on 227 patients (93 %). The remaining 18 patients (7 %) did not undergo a CT scan because of a surgeon's decision or other reasons. Hepatic regeneration rate was calculated in only patients who underwent the postoperative CT scan at days 6–8 after surgery ($n = 29$ in the RH group; $n = 141$ in the RHEBR group). Total volumes of the whole and remnant liver were calculated using Vincent® as previously described (Fujifilm, Tokyo, Japan) [13]. Restitution of liver volume was determined by the percentage of regenerated liver mass and calculated using the following equation: hepatic regeneration rate (%) = 100 × (A − B)/C; in which A is the remnant liver volume at days 6–8 after hepatectomy; B is the calculated remnant liver volume before resection; and C is the whole liver volume before resection.

Statistical analysis

Continuous values were expressed as medians (ranges). After confirming an abnormal data distribution with a Shapiro–Wilk test and Kolmogorov–Smirnov test, a non-parametric Mann–Whitney *U* test was used to evaluate significant differences between patients with and without an extrahepatic bile duct resection. All tests were 2-sided. $p < 0.05$ was considered a statistically significant value. A correlation between two variables was evaluated using a Pearson correlation test. A multivariate analysis was performed using a logistic regression model to determine independent predictors for PHLF incidence and hepatic regeneration rate. To construct a final multivariate logistic regression model, we used a stepwise method with a cutoff value of $p = 0.2$ for inclusion and retention in the model. To calculate the difference in hepatic regeneration rates between the RH and RHEBR groups, we also performed a stepwise linear regression analysis in which potential confounding factors were included and maintained as covariates in the final model with a cutoff value of $p = 0.2$. Analyses were performed with the statistical package SPSS® version 22.0 (SPSS, Chicago, IL, USA).

Results

Clinical features and perioperative factors

Eight-hundreds and eighty consecutive patients who underwent a major hepatectomy from March 2001 to December 2013 were included. Among them, only patients who underwent right hepatectomy were selected ($n = 329$) (Fig. 1). Thereafter, patients with combined pancreatoduodenectomies ($n = 71$), combined resection of other organ ($n = 11$), or laparoscopic hepatectomy ($n = 2$) were excluded, and 245 patients remained. Prospectively collected data from patients with a right hepatectomy (RH, $n = 55$) and RH with an extrahepatic bile duct resection (RHEBR group, $n = 190$) were retrospectively analyzed. The baseline characteristics of the study population were largely different between the RH and RHEBR groups (Table 1). In the RHEBR group, biliary tract cancer accounted for the majority of the diseases, whereas in the RH group, hepatocellular carcinoma and colorectal metastases were the primary diseases.

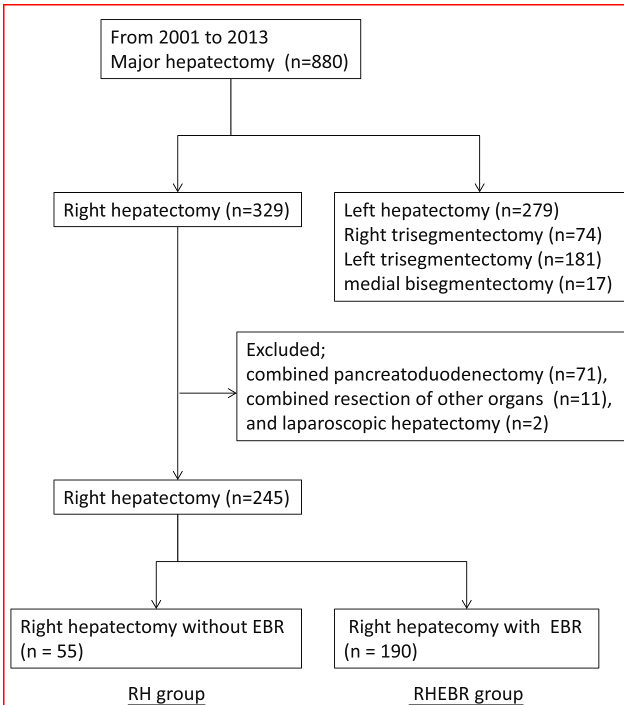

Fig. 1 Flow chart for the study patients. *Note*: major hepatectomy in this study means a resection of three or more Couinaud's segment, excluding the caudate lobe. *EBR* extrahepatic bile duct resection

The percentage of the future liver remnant was not significantly different between the two groups. The median operation time and blood loss were significantly greater in the RHEBR group than in the RH group. Although the overall mortality rate was not different between the two groups, the overall morbidity rate, including the rate of PHLF and infectious complications, was considerably higher in the RHEBR group than in the RH group.

Laboratory data

On postoperative days 5 and 7, the inflammatory factors, such as WBC counts and serum CRP levels, and liver failure-associated factors, such as T-bil and PT-INR, were greater in the RHEBR group than in the RH group (Table 2).

Liver regeneration rate after the hepatectomy

There was no difference in the percentage of liver resection volume between the two groups (58.0 % in the RH group;

Table 1 Clinical features and perioperative factors

	RH ($n = 55$)	RHEBR ($n = 190$)	p value
Preoperative factors			
Median (range) age (years)	58 (23–80)	69 (33-83)	<0.001
Gender (male/female)	33/22	124/66	0.474
Median (range) ICG R15 (%)[a]	8.8 (2.7–23.0)	10.5 (2.6–24.8)	0.026
Child Pugh score B, C	2 (3.6 %)	1 (0.5 %)	0.065
Serum total bilirubin (mg/dl)	0.6 (0.3–1.6)	0.7 (0.3–1.9)	0.290
PT-INR	1.02 (0.90–1.62)	1.01 (0.85–1.98)	0.645
PVE before surgery, *n* (%)	16 (29.1 %)	168 (88.4 %)	<0.001
Type of disease			<0.001
Biliary tract cancer	8 (14.5 %)	158 (83.2 %)	
Hepatocellular carcinoma	19 (34.5 %)	7 (3.7 %)	
Colorectal liver metastases	21 (38.2 %)	5 (2.6 %)	
Others	8 (14.5 %)	18 (9.5 %)	
Intraoperative factors			
Median (range) percentage of resection liver volume (%)[b]	58.0 (16.0–70.1)	54.4 (30.6–71.1)	0.323
Resection of caudate lobe, *n* (%)	7 (12.7 %)	183 (96.3 %)	<0.001
Median (range) operation time (min)	390 (199–884)	555 (322–1262)	<0.001
Median (range) blood loss (ml)	982 (276–6805)	1390 (235–47,200)	0.015
Allogeneic blood transfusion, *n* (%)	13 (23.6 %)	44 (23.2 %)	0.941
Postoperative factors			
Overall mortality, *n* (%)	0 (0 %)	2 (1.1 %)	0.445
Overall morbidity, *n* (%)	10 (18.2 %)	77 (40.5 %)	0.002
PHLF Grade B, C[c], *n* (%)	9 (16.4 %)	75 (39.5 %)	0.001
Bile leakage Grade B, C[c], *n* (%)	5 (9.1 %)	15 (7.9 %)	0.775
Any infectious complications, *n* (%)	2 (3.6 %)	49 (25.7 %)	<0.001
Wound infection, *n* (%)	0 (0 %)	17 (8.9 %)	0.021
Cholangitis, *n* (%)	2 (3.6 %)	77 (40.5 %)	<0.001
Intra-abdominal abscess, *n* (%)	0 (0 %)	43 (22.6 %)	<0.001
Liver abscess, *n* (%)	0 (0 %)	4 (2.1 %)	0.278
Bacteremia, *n* (%)	1 (1.8 %)	16 (8.4 %)	0.090

ICG R15 indocyanine green retention value at 15 min, *PT-INR* prothrombin time-international normalized ratio, *PVE* portal vein embolization, *PHLF* posthepatectomy liver failure

[a] Excluding two patients who did not undergo ICG test and three patients with ICG intolerance

[b] Resection volume was calculated by each surgeon on CT volumetry

[c] According to the definition of International Study Group of Liver Surgery (ISGLS)

54.4 % in the RHEBR group). However, the percentage of newly regenerated liver volume (liver regeneration rate) after the hepatectomy on postoperative days 6–8 was significantly lower in the RHEBR group than in the RH group (median regeneration rate, 14.0 % in the RH group; 7.9 % in the RHEBR group, $p < 0.001$; Fig. 2). One hundred eighty-four patients underwent preoperative PVE ($n = 16$, 29.1 % in the RH group; $n = 168$, 88.4 % in the RHEBR group). To exclude the effects of preoperative PVE, liver regeneration rate was further compared in only patients without preoperative PVE ($n = 18$ in the RH group; $n = 16$ in the RHEBR group). Although the number of patients included in the analysis were small, the regeneration rate still tended to be lower in the RHEBR group (median 10.0 %) as compared to the RH group (median 12.3 %; $p = 0.058$).

Univariate and multivariate analyses for PHLF

In the univariate analysis, a male gender, high ICGR15 (≥20 %), PVE before surgery, type of surgery (i.e., RHEBR), long operation time (≥500 min), great blood loss (≥1000 ml), and blood transfusion were identified to be significant risk factors for the incidence of PHLF (Table 3).

Table 2 Laboratory data

		RH ($n = 55$)	RHEBR ($n = 190$)	p value
WBC	POD 5	4450 (2000–18,600)	6300 (2400–11,700)	0.013
	POD 7	5450 (2400–14,400)	6900 (3000–16,100)	0.001
CRP	POD 5	4.20 (1.16–10.40)	5.33 (1.09–13.71)	0.128
	POD 7	2.71 (0.49–7.52)	4.48 (0.24–11.34)	0.001
T-bil	POD 5	1.1 (0.5–6.3)	1.8 (0.6–21.9)	<0.001
	POD 7	1.0 (0.4–3.2)	1.5 (0.5–24.0)	<0.001
PT-INR	POD 5	1.25 (1.00–1.53)	1.36 (1.08–3.61)	0.003
	POD 7	1.20 (1.08–2.13)	1.34 (1.04–2.62)	0.009

WBC white blood cell counts, *CRP* C-reactive protein, *T-bil* total bilirubin, *PT-INR* prothrombin time-international normalized ratio, *POD* postoperative day

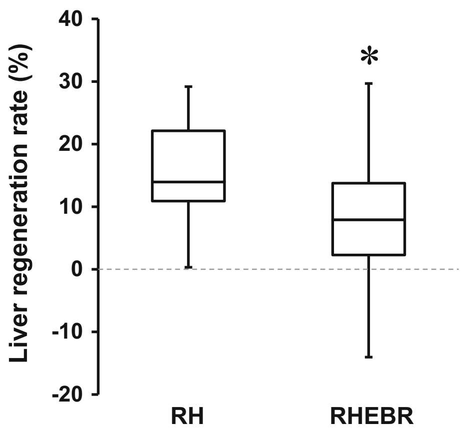

Fig. 2 The percentage of the newly regenerated liver volume (hepatic regeneration rate). The regenerated liver volume 6–8 days after the right hepatectomy were calculated using 3D-CT volumetry and compared with the predicted remnant liver volume on the preoperative CT. The values are expressed as medians (ranges). *$p < 0.001$ versus RH by the Mann–Whitney *U* test

In the multivariate analysis that included the factors with a p value <0.200 in the univariate analysis, a male gender, ICGR15 (≥20 %), type of surgery (RHEBR), and blood transfusion were identified to be independent risk factors for PHLF.

Univariate and multivariate analyses for the impaired liver regeneration rate

The mean liver regeneration rate in the 170 patients who underwent a postoperative CT scan on postoperative days 6–8 was 9.8 %. Therefore, in the next analysis, the risk factors associated with a low liver regeneration rate (<10 %) were examined by univariate and multivariate analyses (Table 4). In the univariate analysis, type of surgery (RHEBR) was the only significant risk factor for an impaired liver regeneration rate following hepatectomy. In the stepwise logistic regression analysis that included and retained the factors with a cutoff value of $p = 0.2$, type of surgery (RHEBR) was the only identified independent risk factor for an impaired liver regeneration rate.

Estimation of the liver regeneration rate in patients with or without an extrahepatic bile duct resection

To estimate the difference in hepatic regeneration rates between the RH and RHEBR groups, we used a stepwise linear regression analysis in which potential confounding factors were included and maintained as covariates in the final model with a cutoff value of $p = 0.2$. In the final model, sex, operation time, bile leakage, WBC counts, T-bil, and PT-INR were selected as covariates. The adjusted hepatic regeneration rate in the RHEBR group was 7.1 % lower (95 % confidence interval 1.8–12.3, $p = 0.011$) than in the RH group.

Discussion

In patients with a perihilar cholangiocarcinoma, a major hepatectomy (either right-side or left-side) with an extrahepatic bile duct resection is a standard procedure to achieve a curative resection [14]. After this procedure, a choledocho-jejunostomy using a Roux-en-Y technique is necessary [9]. Patients who need to undergo a major hepatectomy with an extrahepatic bile duct resection usually have major biliary ductal stenosis. Biliary drainage using an internal or external stent is frequently necessary. Although this procedure reduces symptoms of obstructive jaundice and improves liver function, insertion of a foreign body in a bile duct always causes contamination of biliary duct [15]. During a major hepatectomy with an extrahepatic bile duct resection, contaminated bile may spill over the surgical field. This contamination may lead to superficial/deep/organ space surgical site infections [16].

Table 3 Possible risk factors for the incidence of PHLF (≥grade B) following hepatectomy

	No. of patients	Incidence of PHLF, *n* (%)	Univariable		Multivariable	
			Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value
Age (years)				0.191		
<65	65	18 (27.7)	1.00			
≥65	180	66 (36.7)	1.51 (0.81–2.82)			
Gender				0.010		0.024
Female	88	21 (23.9)	1.00		1.00	
Male	157	63 (40.1)	2.14 (1.19–3.84)		2.24 (1.11–4.49)	
ICGR15 (%)[a]				0.002		0.051
<20	118	29 (24.6)	1.00		1.00	
≥20	123	53 (43.1)	2.32 (1.34–4.03)		1.86 (0.99–3.47)	
Child Pugh				0.234		
A	242	82 (33.9)	1.00			
B, C	3	2 (66.7)	3.90 (0.35–43.68)			
PVE before surgery				0.014		
No	61	13 (21.3)	1.00			
Yes	184	71 (38.6)	2.32 (1.17–4.58)			
Type of surgery				0.001		0.025
RH	55	9 (16.4)	1.00		1.00	
RHEBR	190	75 (39.5)	3.33 (1.54–7.21)		3.02 (1.15–7.91)	
Operation time (min)				<0.001		0.101
<500	98	17 (17.3)	1.00		1.00	
≥500	147	67 (45.6)	3.99 (2.16–7.38)		1.91 (0.88–4.14)	
Blood loss (ml)				<0.001		
<1000	77	10 (13.0)	1.00		1.00	0.128
≥1000	168	74 (44.0)	5.27 (2.54–10.96)		1.95 (0.83–4.58)	
Blood transfusion				<0.001		<0.001
No	188	48 (25.5)	1.00		1.00	
Yes	57	36 (63.2)	5.00 (2.66–9.39)		4.85 (2.34–10.05)	

ICGR15 indocyanine green retention rate at 15 min, *PVE* portal vein embolization, *CI* confidence interval

[a] Excluding two patients who did not undergo ICG test and three patients with ICG intolerance

Moreover, creating a choledocho-jejunostomy and disrupting the system that prevents backflow of enteric bacteria may easily induce regurgitating cholangitis after surgery. These adverse events do not usually occur after a major hepatectomy without an extrahepatic bile duct resection. Therefore, in terms of operation invasiveness, a major hepatectomy with an extrahepatic bile duct resection is largely different from that without an extrahepatic bile duct resection. Nonetheless, these procedures are categorized in a same operative method (i.e., major hepatectomy) in some analysis. To the best of our knowledge, there is no previous large-scale studies that compare clinical outcomes between these two procedures because, in most institutions, the proportion of major hepatectomies with extrahepatic bile duct resections is relatively small compared to that of other hepatectomies. Because the authors' institution is a high volume center for perihilar cholangiocarcinomas and has large number of cases of major hepatectomies with extrahepatic bile duct resections, the outcomes could be compared with a simple hepatectomy in the single institution. The analyzed cases in this study were limited to a right hepatectomy to adjust the level of operative invasiveness as much as possible.

Conventionally, liver resection is classified into "minor" or "major" based on the number of segments removed. In recent years, Lee et al. [17] proposed that liver resection should be classified by the complexity of procedure. Procedures with the highest perceived complexity score all involved the right intersectional plane. However, their study did not differentiate between a concomitant extrahepatic bile duct resection and choledocho-jejunostomy. In the analysis in this study, the addition of an extrahepatic bile duct resection and choledocho-jejunostomy to the right hepatectomy clearly increased mortality,

Table 4 Possible risk factors for the impaired liver regeneration rate following hepatectomy

	No. of patients	Liver regeneration rate <10 %, *n* (%)	Univariable		Multivariable	
			Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value
Age (years)				0.508		
<65	38	19 (50.0)	1.00			
≥65	132	74 (56.1)	1.28 (0.62–2.63)			
Gender				0.527		
Female	64	37 (57.8)	1.00			
Male	106	56 (52.8)	0.82 (0.44–1.53)			
ICGR15 (%)[a]				0.652		
<20	85	48 (57.0)	1.00			
≥20	83	44 (52.8)	0.87 (0.47–1.60)			
Child Pugh				0.893		
A	168	92 (54.8)	1.00			
B, C	2	1 (50.0)	0.83 (0.05–13.43)			
PVE before surgery				0.076		
No	34	14 (41.2)	1.00			
Yes	136	79 (58.1)	1.98 (0.92–4.25)			
Type of surgery				0.001		<0.001
RH	28	7 (25.0)	1.00		1.00	
RHEBR	142	86 (60.6)	4.61 (1.84–11.55)		5.72 (2.20–14.89)	
Operation time (min)				0.120		
<500	60	28 (46.7)	1.00			
≥500	110	65 (59.1)	1.65 (0.88–3.11)			
Blood loss (ml)				0.505		0.125
<1000	53	31 (58.5)	1.00		1.00	
≥1000	117	62 (53.0)	0.80 (0.42–1.54)		0.57 (0.28–1.17)	
Blood transfusion				0.891		
No	128	70 (54.7)	1.00			
Yes	42	23 (54.8)	1.00 (0.50–2.02)			

ICGR15 indocyanine green retention rate at 15 min, *PVE* portal vein embolization, *CI* confidence interval

[a] Excluding two patients who did not undergo ICG test and three patients with ICG intolerance

morbidity, operation time, and intraoperative blood loss compared to the "simple" right hepatectomy. All of the data analyses demonstrated that the major hepatectomy with the extrahepatic bile duct resection should be considered a different procedure from that without the extrahepatic bile duct resection.

This study demonstrated a significantly lower regeneration rate of the remnant liver after surgery in the RHEBR group than in the RH group. The observed difference cannot be simply explained by the procedure of extrahepatic bile duct resection because the clinical backgrounds, including the age, type of disease, and operative invasiveness, which includes operation time and intraoperative bleeding, were largely different between the two groups. Nevertheless, the results of the stepwise linear regression analysis including potential confounding factors indicated that the difference in the type of surgery (i.e., RH vs. RHEBR) is a critical factor for impairment of the liver regeneration capacity following a major hepatectomy. The postoperative levels of serum T-bil and blood PT-INR as well as the incidence rate of PHLF were significantly higher in the RHEBR group than the RH group. It can be speculated that an insufficient liver regeneration following a major hepatectomy with extrahepatic bile duct resection may lead to impaired metabolic and synthetic functions of the liver and may increase the levels of T-bil and PT-INR in the blood, which could increase the incidence of PHLF. Nevertheless, this study did not evaluate a mechanism for impaired liver regeneration in the RHEBR group compared to the RH group. This mechanism may be extremely difficult to elucidate in a clinical setting because there are many differences in the backgrounds of patients who undergo a major hepatectomy with or without an extrahepatic bile duct resection. However, basic research conducted in the authors' institution demonstrated some mechanisms of impaired liver regeneration in a rat model with a 70 % hepatectomy and choledocho-jejunostomy (CJ) [2]. In a rat model with a 70 % hepatectomy and a CJ, the CJ induced severe cholangitis in the periportal area after surgery and suppressed the expression of liver regeneration-associated factors in the liver [2]. These results from the basic research may at least partly explain the mechanisms of a lesser hepatic regeneration rate in the RHEBR group compared to the RH group.

One criticism of this study may be that the two groups of patients differ in many important aspects, as evident from Table 1. The important factors include preoperative ones as age, frequency of preoperative PVE, type of disease as well as intraoperative ones as resection of the caudate lobe, median operation time, and blood loss. Especially, higher proportion of patients with preoperative PVE in the RHEBR group may have an impact on the inferior liver regeneration rate in this group compared to the RH group. However, by the multivariate analysis, PVE was "not" an independent risk factor for PHLF (Table 3) as well as an impaired liver regeneration rate (Table 4).

Using a large number of surgical cases, this study showed a clear difference between the outcomes after a major hepatectomy with and without an extrahepatic bile duct resection. These two procedures should not be included in a same category of procedure when analyzing the clinical outcome. Moreover, the limit of maximum liver resection volume should be differently considered among these two procedures, because of the difference of liver regeneration rate after hepatectomy.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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