Aggressive Surgical Resection for Hilar Cholangiocarcinoma of the Left-Side Predominance

Radicality and Safety of Left-Sided Hepatectomy

Hiroaki Shimizu, MD, Fumio Kimura, MD, Hiroyuki Yoshidome, MD, Masayuki Ohtsuka, MD, Atsushi Kato, MD, Hideyuki Yoshitomi, MD, Katsunori Furukawa, MD, and Masaru Miyazaki, MD

Objectives: To evaluate the clinicopathologic outcomes in patients with hilar cholangiocarcinoma (HC) after left-sided hepatectomy (L-H).

Summary Background Data: L-H is indicated as radical surgery for HC, predominantly involving left hepatic duct. However, several reports have demonstrated that L-H often results in tumor-positive margin and unfavorable prognosis compared with right-sided hepatectomy (R-H).

Methods: A total of 224 patients with HC underwent surgical resection with curative intent at our institution: L-H for Bismuth-Corlette (B-C) type IIIb tumors in 88 patients (39.3%) including 75 left hemihepatectomies and 13 left trisectionectomies, and R-H mainly for B-C type IIIa and IV tumors in 84 patients (37.5%). In this study, clinicopathologic outcomes and perioperative morbidity and mortality rates after L-H were investigated and compared with those after R-H.

Results: Histologically negative margin (R0) resection was achieved in 56 cases (63.6%) with L-H, similar to the results for R-H (58/84, 69.1%). However, the R0 resection rate in L-H cases with portal vein (PV) resection was lower (11/25, 44.0%), and various types of PV reconstruction were required. Proximal ductal stumps and excisional surface at periductal structures were the most common sites of positive margins. However, when curative resection was achieved, 5-year survival was comparable to that in R-H cases. Furthermore, lower mortality was noted in L-H cases, even with left trisectionectomy. Multivariate analysis indicated curability and hepatic artery resection as independent prognostic factors.

Conclusions: Since L-H is a safe procedure and represents the only curative resectional option for type IIIb tumor, aggressive surgical resection should be performed even in cases with PV involvement, if R0 resection is possible.

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Aggressive surgical resection including right or left hemihepatectomy extending to segment 1 has been recognized as a standard treatment option for hilar cholangiocarcinoma (HC).[1–2] However, achieving histologically negative margin (R0) resection remains difficult, although this may offer the only chance for cure and long-term survival.[3–11] Longitudinally, tumor spreading along the bile duct at the proximal side may be a crucial factor for achieving R0 resection.[12–15] Konstadoulakis et al[2] recently reported that tumor-positive margin ratio was significantly higher in cases with left-sided hepatectomy (L-H), as compared with those with right-sided hepatectomy (R-H). Theoretically, L-H for HC may have anatomic disadvantages in terms of radicality, when compared with R-H.[1,2,16,17] The extrahepatic part of the right hepatic duct (remnant side after L-H) is obviously shorter, and the distance from the hepatic bifurcation to the sectional ramification in the right liver is also much shorter than in the left liver.[18] Furthermore, there are so many anatomic variations in the right sectional bile ducts.[19] These anatomic issues may increase the difficulty of achieving tumor-free stumps for right sectional ducts as a part of L-H, when compared with R-H. In addition, vertical tumor spreading, particularly to the right hepatic artery (HA) may represent other important factor for radicality. Since the right HA generally runs just behind the proximal common bile duct, close to the ductal confluence, R-H may have an anatomic advantage for radicality,[11] because en bloc resection of the right HA and surrounding tissue can be performed. Kondo et al[20] have demonstrated that survival in patients treated with right hemihepatectomy was significantly better than that in patients who underwent left hemihepatectomy, isolated caudate lobectomy, or hilar resection alone.

From the viewpoint of anatomic factors at hepatic hilus, L-H for HC is also considered to be a more complicated procedure, and require greater skill, than R-H,[21] especially in cases requiring portal vein (PV) resection and reconstruction. Surgical resection for Bismuth-Corlette (B-C) type IIIb tumor with PV involvement may not yet be a feasible treatment option, even in specialized centers. However, no alternative treatments provide survival comparable with surgical resection. Over the past 20 years, our institution has practiced a policy of aggressive surgical resection of locally advanced HC, even for B-C type IIIb tumor with PV involvement. At present, few detailed studies have analyzed problems with L-H for HC. The present study evaluated the clinicopathologic outcomes and perioperative morbidity and mortality rates in 88 patients with L-H, as well as the intraoperative details, and compared these results to those for 84 patients with R-H.

PATIENTS AND METHODS

Operative Procedures

From April 1984 to September 2008, a total of 224 patients (145 male, 79 female) with HC underwent surgical resection with curative intent at our institution. Mean age at the time of resection was 65 ± 9.4 years (range, 28–82 years). Operative procedures were as follows: R-H mainly for B-C type IIIa and IV tumors in 84 patients (37.5%); L-H for type IIIb tumors in 88 patients (39.3%), including left hemihepatectomy in 75 patients and left trisectionectomy in 13 patients; and parenchyma-preserving hepatectomy,[22] such as caudate lobectomy (S1) and S1 + S4 resection[23] in 26 patients (11.6%), mostly with liver dysfunction. All hepatectomies included caudate lobectomy, hilar resection, and lymph node dissection in the hepatoduodenal ligament and around the pancreas head. Bilioenteric anastomosis was established by Roux-en-Y hepaticojejunostomy with a stent tube (RTBD tube, Sumitomo Bakelite, Tokyo, Japan). Bile duct orifices to be reconstructed in the vicinity of the resected surface of the liver were routinely grouped as

From the Department of General Surgery, Graduate School of Medicine, Chiba University, Chiba Japan.

Reprints: Masaru Miyazaki, MD, Department of General Surgery, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-0856, Japan. E-mail: masaru@faculty.chiba-u.jp.

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much as possible to reduce the number of anastomoses required. Combined vascular resection and reconstruction was performed in 55 of 172 patients who underwent major hepatectomy, PV resection was used in 48 patients (including 4 patients with combined resection of PV and HA resection), and HA resection was used in 11 patients. The decision for vascular resection was made on the basis of intraoperative macroscopic findings of tumor invasion to the vessels, in conjunction with preoperative imaging diagnosis.[15]

Preoperative Assessment

For preoperative clinical assessment, laboratory and imaging workups including ultrasonography, magnetic resonance cholangiopancreatography, mulidetector-row computed tomography, and cholangiography using either percutaneous transhepatic or endoscopic retrograde approach, were performed. Proximal and distal tumor extension to the bile duct were evaluated mainly with direct cholangiography, particularly in patients with obstructive jaundice. Our criteria of irresectability defined by local tumor-related factors were as follows: (1) tumor extension to bilateral secondary PV branches; (2) tumor extension to bilateral secondary HA branches; and (3) expected remnant liver volume less than 30% of the whole liver volume, even after portal embolization (PE). Decisions as to whether R-H or L-H were made on the basis of predominant tumor site, but when both hepatic ducts were invaded equally, R-H was indicated in most cases. Preoperative PE has been performed since 1994 at our institution, when future remnant liver volume was expected to be less than 40% of the whole liver volume. In our series, preoperative PE was performed 14 to 24 days before surgery in 32 of 84 R-H cases (38.1%), and 5 of 88 L-H cases (5.7%).

Patients

Patient background and preoperative parameters, including age, gender, indocyanine green retention rate at 15 minutes, obstructive jaundice (presence/absence), and serum total bilirubin at the time of surgery were assessed in both L-H and R-H cases. As intraoperative parameters, operative time, operative blood loss, number of bilioenteric anastomoses, combined pancreatoduodenectomy, and PV resection and reconstruction were evaluated. Postoperative complications were also examined. Bilioenteric anastomotic leakage was diagnosed by cholangiographic demonstration of leak from the anastomosis via the biliary stent tube placed during surgery. In addition, pathologic findings in resected specimens were evaluated using the TNM Classification of Malignant Tumors by the International Union Against Cancer classification (sixth edition, 2002). Curative (R0) resection was defined as histologically negative surgical margins at the proximal (hepatic-side) stump of the bile duct, distal (duodenal-side) stump of the bile duct, and excisional surface. Postoperative complications and survival were also analyzed.

Statistics

Results are expressed as the mean ± SD. Statistical analyses were performed using the χ^2 test and the Fisher exact probability test, where appropriate. Statistical analysis of patient survival was undertaken using the Kaplan-Meier method. Comparison of patient survival between groups was performed using the log-rank test. Multivariate regression analysis of factors related to survival was carried out using the Cox proportional hazard model. $P < 0.05$ was considered statistically significant. Statistical calculations were performed using SPSS software (SPSS, Inc, Chicago, IL).

TABLE 1. Patients Characteristics and Clinicopathologic Features

	Right-Sided Hepatectomy (n = 84)	Left-Sided Hepatectomy (n = 88)
Age (yr)	67.1 ± 8.0 (48–79)*	67.0 ± 8.9 (40–73)
Gender (men:women)	47:37	61:27
ICG-R15 (%)	16.1 ± 8.9	12.9 ± 8.9
Obstructive jaundice (−/+)	13:71	16:72
Total bilirubin at operation (mg/dL)	1.8 ± 1.3	1.7 ± 1.2
Operative time (min)	483 ± 106	522 ± 101
Operative blood loss (mL)	2257 ± 2326	2090 ± 1840
Blood transfusion (+/−)	53:31	67:21
No. bilioenteric anastomosis	2.20 ± 0.7	2.53 ± 1.0
Pancreatoduodenectomy (+/−)	2:82	1:87
Portal vein resection (+/−)	23:61	25:63
Hepatic artery resection (+/−)	2:82	9:79
G1/G2/G3	22:47:15	34:39:15
Lymph node metastasis (+/−)	49:35	37:51
Lymphatic vessel invasion (+/−)	76:8	70:18
Venous invasion (+/−)	71:13	62:26
Perineural invasion (+/−)	76:8	75:13
Stage I/II/III/IV†	8:39:29:8	10:38:32:8

*Mean ± SD (range).
†According to UICC, 6th edition.

RESULTS

Patient Characteristics and Clinicopathologic Features

Patient characteristics and clinicopathologic features are shown in Table 1. No significant differences were apparent between L-H and R-H cases in terms of age, gender, indocyanine green retention rate at 15 minutes, obstructive jaundice (presence/absence), or total bilirubin levels at the time of operation. No significant differences in operative parameters such as operative time, operative blood loss, blood transfusion, combined pancreatoduodenectomy, or combined vascular resection were found between groups. The number of bilioenteric anastomoses tended to be higher in L-H cases than in R-H cases, but this difference was not significant. Histopathologic findings in resected specimens, including differentiation of tumors, lymph node involvement, and stage grouping, based on the International Union Against Cancer classification (sixth edition) were not significantly different between L-H and R-H cases.

Operative Curability

R0 resection was obtained in 56 of 88 patients (63.6%) with L-H (left hemihepatectomy, 48 of 75 patients [64.0%]: left trisectionectomy, 8 of 13 patients [63.6%]), compared with 58 of 84 patients (69.1%) with R-H (right hemihepatectomy, 51 of 77 [66.2%]; right trisectionectomy, 7 of 7 [100%]). Proximal ductal stumps were the most common margin positive sites after both cases with L-H (71.9%) and R-H (65.4%) (Table 2). In particular, high rates were noted with left hemihepatectomy (74.1%, 20/27). Positive dissected margins at periductal structures were also more frequent in

TABLE 2. Surgical Margin Positive Sites After Right- or Left-Sided Hepatectomy

Hepatectomy (n)	Surgical Margin Positive (R1) Resection	pHM(+)*	pDM(+)*	pEM(+)†
Right-sided hemihepatectomy (77)	26	17 (65.4%)	8 (30.8%)	7 (26.9%)
Right-sided trisectionectomy (7)	0	0	0	0
Total	26	17 (65.4%)	8 (30.8%)	7 (26.9%)
Left-sided hemihepatectomy (75)	27	20 (74.1%)	7 (25.9%)	15 (55.5%)
Left-sided trisectionectomy (13)	5	3 (60%)	1 (20%)	4 (80%)
Total	32	23 (71.9%)	8 (25.0%)	14 (59.4%)

*Ductal margin at hepatic cut end (pHM), duodenal cut end (pDM).
†Dissected margin at periductal structures (pEM).

TABLE 3. Portal Vein Reconstruction Methods

Hepatectomy	(n)
Right-sided hepatectomy	23
Segmental resection	23
End-to-end anastomosis	21
Left renal vein interposition graft	2
Left-sided hepatectomy	25
Segmental resection	9
End-to-end anastomosis	7
Left renal vein interposition graft	2
Wedge resection	16
Direct closure	13
Inferior mesenteric vein patch graft	1
Patch repair (using right-sidewall of RA-PV*)	2†

*RA-PV, right anterior branch of portal vein.
†Left trisectionectomy cases.

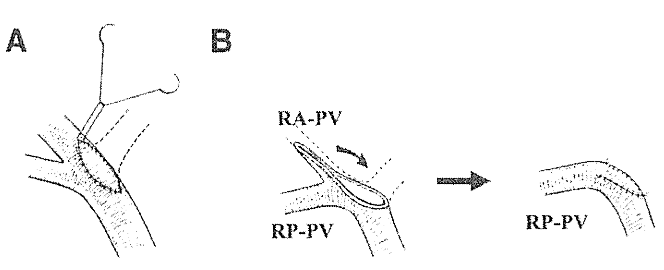

FIGURE 1. Methods of portal vein reconstruction after wedge resection of portal bifurcation after left-sided hepatectomy for hilar cholangiocarcinoma. A, Inferior mesenteric vein patch graft. B, Patch repair using right-side wall of the right anterior branch of the portal vein (RA-PV) in left trisectionectomy. RP-PV, right posterior branch of the portal vein.

L-H cases (59.4%) than in R-H cases (26.9%). Among patients with combined PV resection and reconstruction, curative resection was achieved in 16 of 23 patients (69.6%) with R-H, but only in 11 of 25 patients (44.0%) with L-H. PV was reconstructed in an end-to-end fashion in most cases with R-H (Table 3). However, various types of PV reconstruction were performed in cases with L-H, with end-to-end reconstruction in 7 cases and left renal vein interposition graft in 2 cases after PV segmental resection. Furthermore, after wedge resection of the portal bifurcation, direct closure was performed in 13 cases, inferior mesenteric vein patch graft to close a large defect (Fig. 1A) in 1 case, and patch repair using the intact right-side wall of the right anterior PV (Fig. 1B) in 2 cases of left trisectionectomy.

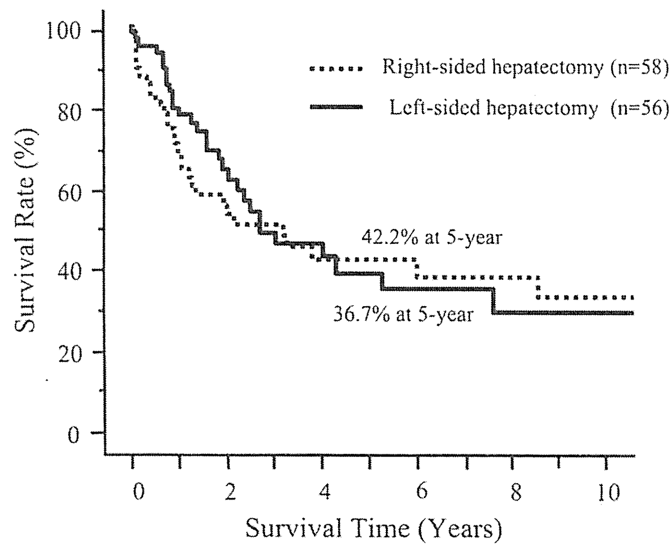

FIGURE 2. Survival curves after curative (R0) resection in patients undergoing right- or left-sided hepatectomy for hilar cholangiocarcinoma.

Postoperative Survival and Surgical Morbidity and Mortality

Overall 5-year survival rates including hospital deaths were 28.3% (median survival: 16.3 months) in L-H cases and 30.3% (median survival, 14.2 months) in R-H cases. Among the patients who underwent R0 resection, 3- and 5-year survival rates were 46.0% and 36.7% (median survival, 24.4 months) in L-H cases, and 50.9% and 42.2% (median survival, 14.1 months) in R-H cases, respectively (Fig. 2). Furthermore, in R0 cases with PV resection and reconstruction, 5-year survival rates in L-H and R-H cases were 38.2% (median survival, 20.0 months) and 26.7% (median survival, 10.7 months), respectively, with no significant differences (Fig. 3).

Surgical morbidity and mortality are shown in Table 4. Morbidity rate for L-H cases (40.9%) was almost the same as for R-H cases (47.6%). However, bilioenteric anastomotic leakage occurred in 16 of 88 patients (18.2%) in L-H cases, but only 8 of 84 patients (9.5%) in R-H cases. Conversely, hyperbilirubinemia and pleural effusion were observed much more frequently in R-H cases. Furthermore, 9 deaths occurred in 84 R-H cases (10.7%), compared with only 2 in 88 L-H cases (2.3%), although this difference was not statistically significant.

Uni- and Multivariate Analysis of Prognostic Factors

Univariate analysis of survival identified curability, lymphatic vessel invasion, venous invasion, PV resection, and HA

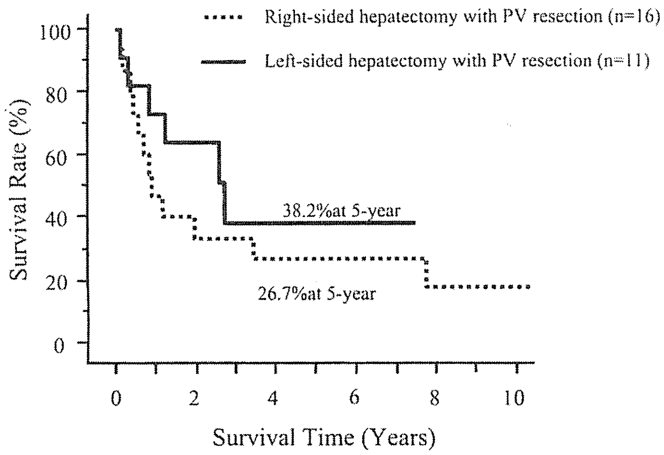

FIGURE 3. Survival curves after curative (R0) resection in patients undergoing right-sided hepatectomy with portal vein resection or left-sided hepatectomy with portal vein resection for hilar cholangiocarcinoma.

TABLE 4. Surgical Morbidity and Mortality After Right- or Left-Sided Hepatectomy

	Right-Sided Hepatectomy (n = 84)	Left-Sided Hepatectomy (n = 88)
Morbidity	40 (47.6%)	36 (40.9%)
Wound infection	12	9
Pleural effusion	18	12
Bile leak from liver stump	4	9
Hyperbilirubinemia	17	8
Intra-abdominal abscess	8	5
Bilioenteric anastomotic leakage	8	16
Sepsis	10	9
Pneumonia	6	5
Rupture of pseudoaneurysm	2	1
Portal vein thrombus	2	1
Renal failure	1	1
Mortality rate	9 (10.7%)	2 (2.3%)
Operative death	2	1
Hospital death	7	1

resection as significant prognostic factors in patients who underwent L-H (Table 5). Multivariate analysis revealed only 2 independent factors influencing survival after L-H: curability and HA resection (Table 6). In contrast, although 5 factors were identified by univariate analysis as significant prognostic factors in patients who underwent R-H (Table 7), multivariate analysis demonstrated curability, lymph node metastasis, and HA resection as independent prognostic factors (Table 8).

DISCUSSION

Advanced HC is a significant therapeutic challenge for biliary surgeons, as negative margin (R0) resection is the most important factor for long-term survival.[2–12] To achieve R0 resection, an appropriate operative procedure based on preoperative evaluation of tumor extension along the bile duct, particularly at the proximal side, is crucial for patients with HC. Furthermore, detailed evaluation of biliary anatomy at hepatic hilus is also required not only for good orientation during surgery, but also to ensure negative ductal margins, especially in cases of L-H,[21] due to greater anatomic variability on this side. Although decisions on whether to perform R-H or L-H should be made according to the predominant tumor site, L-H may have an anatomic disadvantage for curability, as

TABLE 5. Univariate Analysis of Survival in Patients Undergoing Left-Sided Hepatectomy

Factors (n)	Survival Rate % (n) 3-yr	5-yr	*P*
Age			0.848
<70 (63)	38.1 (14)	28.3 (9)	
>70 (25)	36.1 (6)	30.1 (2)	
Gender			0.371
Men (61)	32.7 (12)	24.2 (7)	
Female (27)	47.1 (8)	35.3 (3)	
Curability			<0.0001
R0 (56)	46.0 (18)	36.7 (10)	
R1 (32)	14.7 (2)	0 (0)	
Lymph node metastasis			0.157
Negative (51)	44.1 (16)	32.0 (9)	
Positive (37)	28.9 (4)	28.9 (1)	
Lymphatic invasion			0.049
Negative (18)	67.0 (7)	53.6 (4)	
Positive (70)	29.7 (13)	22.4 (6)	
Venous invasion			0.004
Negative (26)	72.4 (9)	54.3 (6)	
Positive (62)	25.6 (11)	20.9 (4)	
Perineural invasion			0.128
Negative (13)	65.9 (6)	44.3 (4)	
Positive (75)	31.2 (14)	26.7 (6)	
Differentiation			0.748
G1, G2 (73)	36.1 (16)	30.1 (8)	
G3 (15)	44.0 (4)	22.0 (2)	
PV resection			0.020
Negative (63)	42.0 (17)	32.7 (9)	
Positive (25)	22.6 (3)	15.1 (1)	
HA resection			0.0005
Negative (79)	40.3 (20)	30.6 (10)	
Positive (9)	0 (0)	0 (0)	

PV indicates portal vein; HA, hepatic artery.

TABLE 6. Multivariate Analysis of Survival in Patients Undergoing Left-Sided Hepatectomy

Factors	Relative Risk	95% Confidence Intervals Lower	Upper	*P*
Curability	2.560	1.317	4.975	0.006
Lymphatic vessel invasion	1.279	0.479	3.409	0.623
Venous invasion	1.833	0.717	4.690	0.206
PV resection	1.165	0.593	2.288	0.657
HA resection	3.063	1.289	7.282	0.011

PV indicates portal vein; HA, hepatic artery.

TABLE 7. Univariate Analysis of Survival in Patients Undergoing Right-Sided Hepatectomy

Factors (n)	Survival Rate % (n) 3-yr	5-yr	P
Age			0.512
<70 (58)	42.8 (14)	33.1 (8)	
>70 (26)	42.8 (7)	24.4 (3)	
Gender			0.951
Men (47)	40.5 (9)	25.7 (5)	
Female (37)	44.2 (12)	33.2 (6)	
Curability			0.032
R0 (58)	50.9 (18)	42.2 (11)	
R1 (26)	24.5 (3)	0 (0)	
Lymph node metastasis			<0.0001
Negative (35)	68.0 (13)	56.1 (7)	
Positive (49)	27.3 (8)	13.6 (4)	
Lymphatic vessel invasion			0.045
Negative (8)	87.5 (4)	65.6 (2)	
Positive (76)	38.6 (17)	26.9 (9)	
Venous invasion			0.165
Negative (13)	59.8 (3)	59.8 (2)	
Positive (71)	40.9 (18)	26.5 (9)	
Perineural invasion			0.126
Negative (8)	70.0 (2)	70.0 (2)	
Positive (76)	40.7 (19)	27.3 (9)	
Differentiation			0.471
G1, G2 (69)	47.6 (20)	32.7 (10)	
G3 (15)	20.8 (1)	20.8 (1)	
PV resection			0.018
Negative (61)	51.5 (16)	34.5 (8)	
Positive (23)	26.8 (5)	21.4 (3)	
HA resection			<0.0001
Negative (82)	44.2 (21)	31.0 (11)	
Positive (2)	0 (0)	0 (0)	

PV indicates portal vein; HA, hepatic artery.

TABLE 8. Multivariate Analysis of Survival in Patients Undergoing Right-Sided Hepatectomy

Factors	Relative Risk	95% Confidence Intervals Lower	Upper	P
Curability	2.413	1.303	4.467	0.005
Lymph node metastasis	2.869	1.463	5.630	0.002
Lymphatic vessel invasion	3.011	0.706	12.84	0.136
PV resection	1.776	0.968	3.258	0.064
HA resection	16.31	2.951	90.13	0.001

PV indicates portal vein; HA, hepatic artery.

compared with R-H.[1,2,16,17] Accordingly, tumor-free stumps of the right segmental ducts as a part of L-H are more likely to be difficult to achieve, because distance from the hepatic bifurcation to the right segmental ramification is obviously shorter than that to the left ramification.[18] However, our series identified no significant differences in curability or postoperative survival between patients undergoing L-H and R-H. Interestingly, R0 resection was achieved in all 7 patients who underwent right trisectionectomy, but in only 8 of 13 patients (61.5%) who underwent left trisectionectomy. This suggests that a more extended resection from the right side, but not from left side may provide greater potential for curability.

HC often requires combined PV resection and reconstruction to achieve negative margins,[12,13,15,24] although most patients with HC are treated with unilateral hepatectomy. At present, combined PV resection and reconstruction are recognized as a means of increasing resectability with acceptable mortality,[13,15] and may provide better chances for long-term survival.[12,13,15] Although several authors[12,13,16,17] have already described surgical outcomes of major hepatectomy combined with PV resection and reconstruction, few reports have discussed differences in surgical curability between R-H and L-H cases. In our series, surgical curability in patients undergoing L-H with PV resection and reconstruction was lower (11/25, 44.0%) than in R-H cases (16/23, 69.6%). Furthermore, in most R-H cases, end-to-end anastomosis was possible after segmental resection of the right PV including the portal bifurcation, since the extrahepatic portion (called the transverse portion) of the left PV is sufficiently long. However, in L-H cases, end-to-end anastomosis may not be as easy, because of the limited mobilization of the right PV. PV resection and reconstruction design may thus be important for successful vascular reconstruction. It should be decided based on the extent of PV involvement and anatomic variation of the PV confluence at the hepatic hilus. For example, in cases with PV triple confluence or cases with a right posterior sectional branch joining the portal trunk, PV wedge resection with direct closure or patch graft repair may be more applicable, unless the portal bifurcation is not invaded circumferentially by the tumor. In our series, various types of PV resection and reconstruction were performed (Table 3). After segmental PV resection, end-to-end reconstruction was performed in 9 cases, including 2 cases of left renal vein interposition graft. After wedge resection of PV bifurcation, direct closure was performed in 13 cases, inferior mesenteric vein patch graft in 1 case (Fig. 1A) and patch repair with the right-side wall of the right anterior PV in 2 cases of left trisectionectomy (Fig. 1B).

Postoperative morbidity rates were almost the same between L-H and R-H cases. However, the mortality rate in patients with L-H was 2.3%, appearing much better than that in patients with R-H (10.7%). Anastomotic leakage occurred in 16 of 88 patients (18.2%) among L-H cases, but only 8 of 84 patients (9.5%) among R-H cases, although operation time and the number of bilioenteric anastomoses were similar between the 2 groups. These results suggest that bilioenteric anastomosis might be technically more difficult in L-H cases, probably due to the deep position. In particular, the orifice of the right posterior sectionary duct is located behind the right PV after left hemihepatectomy.

In our series, operative curability and postoperative survival in patients undergoing L-H were not inferior to those in patients undergoing the R-H. Moreover, operative mortality tended to be lower in L-H cases, although incidence of anastomotic leakage was more frequent than in R-H cases. L-H for HC is generally considered to be a more complicated procedure, requiring greater skill, particularly in cases requiring PV resection and reconstruction. However, no alternative treatments provide comparable survival to surgical resection. We thus believe that L-H should be aggressively performed for type IIIb tumor, if curative resection is possible, even in cases with portal involvement.

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TOPICS

A new era of surgical treatment of hilar cholangiocarcinoma: comparison of leading Eastern and Western centers

One hundred seven consecutive surgical resections for hilar cholangiocarcinoma of Bismuth types II, III, IV between 2001 and 2008

Masaru Miyazaki · Fumio Kimura · Hiroaki Shimizu · Hiroyuki Yoshidome · Masayuki Otuka · Atushi Kato · Hideyuki Yoshitomi · Katsunori Furukawa · Dan Takeuchi · Tsukasa Takayashiki · Kousuke Suda · Shigetugu Takano

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Abstract Many authors at high-volume centers all over the world have reported improved outcomes of hilar cholangiocarcinoma by several aggressive surgical approaches such as extended hepatic resection, combined vascular resection, and hepatopancreaticoduodenectomy in recent years. There has been great progress in the surgical treatment of hilar cholangiocarcinoma with these previous efforts by aggressive hepatobiliary surgeons. In particular, surgical techniques, diagnostic modalities, and perioperative management have been remarkably improved as compared with before. Herein we report the surgical outcome for both hilar cholangiocarcinoma of Bismuth types II, III, and IV and intrahepatic cholangiocarcinoma involving the hepatic duct confluence during the recent 8-year period between 2001 and 2008 at our institution, the Department of General Surgery at Chiba University. From our recent experienced results, it can be concluded that the surgical strategy for hilar cholangiocarcinoma has been improved remarkably, and major surgical hepatectomy can be done with relative safety, and these aggressive surgical approaches, including combined vascular resection, may be warranted for the surgical treatment of hilar cholangiocarcinoma. However, the adoption of new innovative therapeutic approaches might be required for further improvement of surgical outcome of hilar cholangiocarcinoma.

M. Miyazaki (✉) · F. Kimura · H. Shimizu · H. Yoshidome · M. Otuka · A. Kato · H. Yoshitomi · K. Furukawa · D. Takeuchi · T. Takayashiki · K. Suda · S. Takano
Department of General Surgery,
Graduate School of Medicine, Chiba University,
1-8-1, Inohana, Chuou-ku, Chiba 260-0856, Japan
e-mail: masaru@faculty.chiba-u.jp

Keywords Hilar cholangiocarcinoma · Surgical resection · Hepatectomy · Vascular resection

Introduction

Especially, in hilar cholangiocarcinoma among biliary tract carcinomas, it is still very difficult to achieve a favorable outcome by surgical resection. Most patients with hilar cholangiocarcinoma are diagnosed at too advanced a stage to be radically resected. Many authors at high-volume centers all over the world have reported improved outcomes of hilar cholangiocarcinoma by several aggressive surgical approaches such as extended hepatic resection, combined vascular resection, and hepatopancreaticoduodenectomy in recent years [1–6]. There has been great progress in the surgical treatment of hilar cholangiocarcinoma with these previous efforts by aggressive hepatobiliary surgeons. In particular, surgical techniques, diagnostic modalities, and perioperative management have been remarkably improved as compared with before. Herein we report the surgical outcome for hilar cholangiocarcinoma during the recent 8-year period between 2001 and 2008 at our institution, the Department of General Surgery at Chiba University.

Patients and methods

Patients

Between January 2001 and December 2008, 107 patients with hilar cholangiocarcinoma underwent surgical resection at our institution. These 107 consecutive patients were the subjects of this study. Hilar cholangiocarcinoma in this series was defined as both extrahepatic bile duct carcinoma involving the hepatic hilar bile duct confluence (namely, Bismuth types [7] II, III, and IV, excluding type I) and intrahepatic cholangiocarcinoma involving the hepatic hilar bile duct confluence.

Preoperative biliary drainage was performed routinely for the patients with obstructive jaundice through nasobiliary or percutaneous transhepatic routes. One hundred two of the 107 resected patients underwent preoperative biliary drainage for the relief of obstructive jaundice and for correct evaluation of cancer extension. Our criteria for unresectability, defined by local, tumor-related factors, were as follows: (1) tumor extension far over bilateral secondary biliary radicals; (2) tumor extension to bilateral secondary portal vein branches; and (3) tumor extension to bilateral secondary hepatic artery branches. The surgical unfitness of the patient, excluding tumor extension factors, was evaluated by factors including age, gender, serum total bilirubin level, activities of daily life, and future remnant liver volume after hepatectomy.

Preoperative portal vein embolization was generally carried out 14–28 days before operation in the 20 patients in whom the remnant liver volume after surgical resection was expected to be less than 40% of the whole liver volume. The portal vein branch was embolized via the ileocolic vein, after minilaparotomy performed under lumbar anesthesia.

Postoperative complications and survival were analyzed according to the Kaplan–Meier method. Operative mortality in this series was defined as death within 60 days during the hospital admission.

Surgical procedures

Operative procedures were selected according to the preoperative evaluation of local tumor extent by imaging findings and the preoperative evaluation of physical surgical fitness. Curative resection was defined as a histologically negative surgical margin at the hepatic stump of the bile duct, duodenal stump of the bile duct, and the excisional surface. As previously reported, parenchyma-preserving hepatectomy [8] and parenchyma-preserving extensive hilar bile duct resection [9] were chosen to limit surgical resection as much as possible to the extent that was necessary for curative purposes, especially in patients with comorbid medical conditions indicating increased operative risk. Combined vascular resection was carried out in 28 of the 107 patients, as shown in Table 4. The decision to perform combined vascular resection was made mainly according to the preoperative imaging in conjunction with the intraoperative macroscopic findings of tumor invasion to the vessels. The portal vein was reconstructed in an end-to-end fashion in 22 out of 25 patients (88%), and autologous vein grafts using a left renal vein [10] were employed in three patients (12%). The right hepatic artery was combinedly resected and reconstructed in an end-to-end fashion in three patients. The hepatic vein and/or inferior vena cava was resected in seven patients.

Table 1 Bismuth classifications of hilar cholangiocarcinoma in patients who underwent surgical resection between January 2001 and December 2008

Bismuth type	Number of patients
II	18
IIIa	20
IIIb	24
IV	45
Total	107

Pancreaticoduodenectomy was also combinedly performed with hepatectomy in six patients. All operative procedures included resection of the extrahepatic bile duct and gallbladder with bilioenteric bypass using a Roux-en-Y jejunal loop.

Statistical analysis

Statistical analysis of survival was carried out according to the Kaplan–Meier method. Comparison of patient survivals in the different groups was carried out using the log-rank test. Significance was established at $P < 0.5$.

Results

Patients' characteristics and surgical operative procedures

The patients' ages ranged from 27 to 80 years (median 68 years). There were 69 men and 38 women. Bismuth's classification of hilar cholangiocarcinoma in the hundred seven patients showed 18 of type II, 20 of type IIIa, 24 of type IIIb, and 45 of type IV (Table 1). Preoperative portal vein embolization was done in 20 patients. In 15 of the 38 patients who were expected to undergo right hemihepatectomy and 5 out of 11 patients who were expected to undergo left trisegmentectomy, the branch of portal vein of the future resected segments of the liver was embolized (Table 2). Various surgical procedures were selected to carry out radical resection. Extended hilar bile duct resection using a transhepatic anterior approach was done in 10 patients with hilar cholangiocarcinoma that was well localized at the hepatic duct confluence. The other 97 patients underwent various kinds of hepatic resection including parenchyma-preserving hepatectomy, left-sided hepatectomy, and right-sided hepatectomy (Table 3).

Table 2 Preoperative portal vein embolization

Hepatectomy procedures	Portal vein embolization (%)
Right-sided hepatectomy	
Right hemihepatectomy	15/38 (39)*
Right trisegmentectomy	0/1 (0)
Total	15/39 (38)**
Left-sided hepatectomy	
Left hemihepatectomy	0/37 (0)*
Left trisegmentectomy	5/11 (45)
Total	5/48 (10)**

** $P < 0.01$, * $P < 0.001$

Table 3 Operative procedures in 107 consecutive surgical resections for hilar cholangiocarcinomas

Vessels	Number of patients
Hilar bile duct resection	10
Hepatectomy	97
S_1-resection[a]	4
$S_1 + S_4$ resection	5
Central bisegmentectomy	1
Left hemihepatectomy	37
Left trisegmentectomy	11
Right hemihepatectomy	38
Right trisegmentectomy	1
Total	107

[a] *S* segment according to the Couinaud classification

Combined vascular resections were done in 25 patients for the portal vein, 7 patients for the inferior vena cava and hepatic vein, and three patients for the right hepatic artery. In the 25 portal vein resections, end-to-end reconstruction was done in 22 patients, and segmental grafts using a left renal vein were done in three patients. The right hepatic artery was reconstructed in three patients in an end-to-end fashion. Eight hepatic veins and/or inferior vena cava resections were repaired with primary closure in four patients, and with patch repair using an autologous vein graft in three patients (Table 4).

Histological curability and operative mortality

There were 63 curative surgical resections in the 107 patients who underwent surgical resection in this study series. The surgical curability in the right-sided hepatectomy group was significantly higher than that in the left-sided hepatectomy and extensive hilar bile duct resection groups ($P < 0.05$). There was no difference between parenchyma-preserving hepatectomy and right or left-sided hepatectomy (Table 5). There were two in-hospital deaths after surgical resection. One patient died of septic complications at 30 days after right hemihepatectomy with portal vein resection. This patient had preoperatively persistent cholangitis despite multiple biliary drainages. After surgery the patient experienced septic shock and did not recover from sepsis. The other patient died of rupture of a pseudoaneurysm in the right hepatic artery after left hemihepatectomy and subsequent hepatic failure at 47 days after surgery. The surgical mortality rate in this series was 1.9% (two out of 107 patients; Table 6).

Table 4 Combined vascular resection in 107 consecutive surgical resections for hilar cholangiocarcinoma

Vessels	Number of patients
Portal vein	25
End-to-end	22
Autologous vein graft	3
Hepatic vein and inferior vena cava	7
Primary closure	4
Autologous vein graft	3
Hepatic artery	3
Right hepatic artery	3

Table 5 Histological curability in 107 consecutive surgical resections for hilar cholangiocarcinoma

Hepatectomy procedures	Surgical curability (%)
Right-sided hepatectomy	29/39 (74)*,**
Left-sided hepatectomy	24/48 (50)*
Parenchyma-preserving hepatectomy	6/10 (60)
Extensive hilar bile duct resection	4/10 (40)**
Total	63/107 (59)

*, ** $P < 0.05$

Table 6 Operative mortality after 107 consecutive surgical resections for hilar cholangiocarcinoma

Hepatectomy procedures	Operative mortality
Right-sided hepatectomy	1/39 (2.6%)
Left-sided hepatectomy	1/48 (2.1%)
Parenchyma-preserving hepatectomy	0/10
Extensive hilar bile duct resection	0/10
Total resection	2/107 (1.9%)

Operative mortality was defined as death within 60 days during the hospital admission

Survival

Survival rates in the curative resection group were 73, 50, and 33% at 1, 3, and 5 years after surgery, and were not

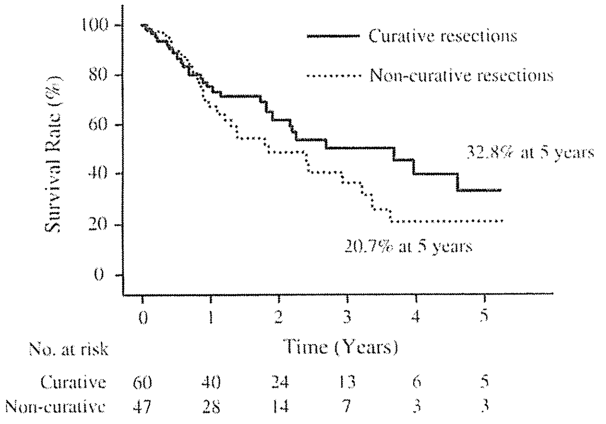

Fig. 1 Survival of patients who underwent curative and noncurative resection for hilar cholangiocarcinoma, after surgical resection. There was no significant difference between the two groups

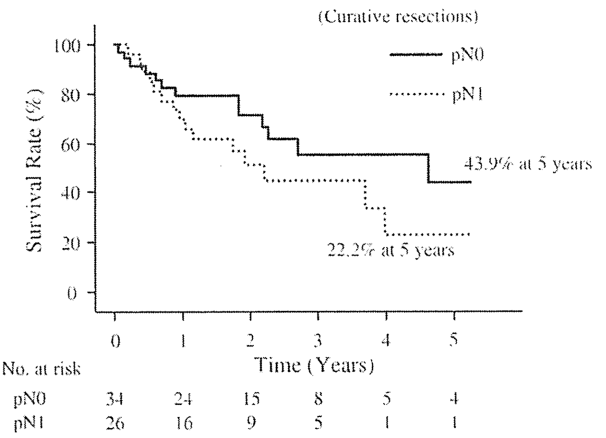

Fig. 2 Survival of patients who underwent curative resection. Comparison of survival rates between the groups with positive and negative lymph node involvement. No significant difference was found between the two groups

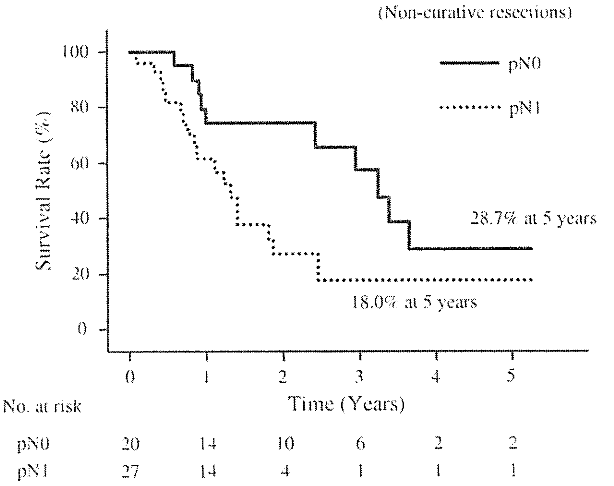

Fig. 3 Survival of patients who underwent noncurative resection. Comparison of survival rates between the groups with positive and negative lymph node involvement. There was a significant difference between the two groups ($P < 0.05$)

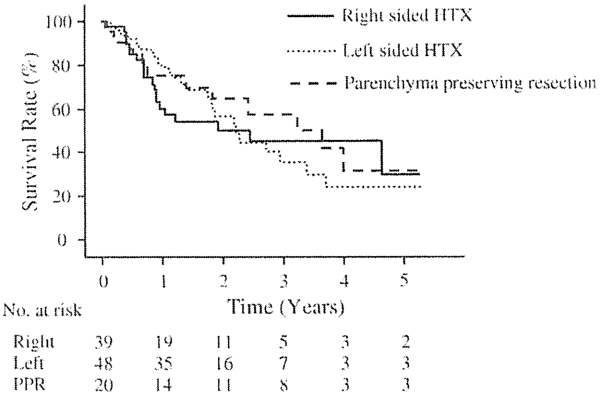

Fig. 4 Survival of the patients who underwent surgical resection. Comparison of survival rates among three groups; those with right-sided hepatectomy (*HTX*), those with left-sided hepatectomy, and those with parenchyma-preserving resection (*PPR*). There were no significant differences among the three groups

significantly different from the survival rates in the noncurative resection group, at 67, 36, and 21% at 1, 3, 5 years, respectively (Fig. 1). In the patients with a curative resection, the survival rates in the group without lymph nodal involvement were 79, 55, and 44% at 1, 3, and 5 years, and these rates were not significantly different from those in the group with lymph nodal involvement, at 65, 44, and 22% at 1, 3, and 5 years, respectively (Fig. 2). On the contrary, in the patients with noncurative resection, the survival rates in the group without lymph nodal involvement were markedly better than those in the group with lymph nodal involvement, at 74, 58, and 29% versus 62, 18, and 18% at 1, 3, and 5 years, respectively ($P < 0.05$; Fig. 3). As to the relationship between survival and the hepatectomy procedures, there were no significant differences among the three hepatectomy groups: right-sided hepatectomy, left-sided hepatectomy, and parenchyma-preserving resection, at 57, 45, and 30%; 79, 36, and 24%; and 75, 57, and 31% at 1, 3, and 5 years, respectively (Fig. 4).

The parenchyma-preserving resection group included the two groups of parenchyma-preserving hepatectomy and extensive hilar bile duct resection.

Discussion

There have been many efforts by several surgeons until the present time to improve the prognosis in patients with hilar cholangiocarcinoma. Of the therapeutic modalities for patients with cholangiocarcinoma, surgical resection is still the only hope for cure [11]. Therefore, hepatobiliary surgeons have tried to employ surgical resection for patients with hilar cholangiocarcinoma despite the presence of advanced carcinoma. Tsao et al. [12] have reported that patients who underwent noncurative resection had a better survival than that of unresectable patients. However, as these comparisons included various patients with different tumor stages, it seems to be difficult and unclear to compare the outcome of the patients undergoing noncurative resection with that of unresectable patients. In the present study series from January 2001 to December 2008, the survival of the patients who underwent noncurative resection was 21% at 5 years after surgery. This survival rate appears to be not so bad as compared with the survival rates in the unresectable patients that have been reported previously by many institutions [1–6, 12]. As a significant prognostic factor after surgical resection in patients with hilar cholangiocarcinomas, surgical curability has been revealed to be important in many reports [13–15]. Also, we have previously revealed curative resection, lymph node involvement, and combined vascular resection as significant prognostic factors after surgical resection [8]. However, in the present series of the last consecutive 107 patients who underwent surgical resection, there was no difference in survival between the two groups who had curative and noncurative resections. The reason for this lack of difference in survival may be due to the short observation period in the last experienced series, or it may be due to the effects of the introduction of a chemotherapeutic strategy. We have recently employed adjuvant cancer chemotherapy for the patients in whom the surgery resulted in noncurative resection.

The lymph node involvement significantly affected the survival in the patients undergoing non-curative resection as shown in Fig. 3. However, it was not shown as a significant prognostic factor in the patients undergoing the curative resection as shown in Fig. 2. From these results in our series, it should be noticed that the existence of lymph node involvement is not always a criteria of unresectability for hilar cholangiocarcinoma. However, this result shows that the existence of lymph node involvement more strongly affected the prognosis of the patients who underwent the noncurative resection than the prognosis of the patients who underwent the curative resection. Therefore, these results do not exclude the significance of lymph node involvement as a prognostic factor after surgical resection in patients with hilar cholangiocarcinoma.

The procedure of hepatectomy has been reported to affect surgical curability. A right-sided hepatectomy has some advantages for obtaining a curative resection for hilar cholangiocarcinoma [1, 2, 16]. The first advantage is that the right hepatic artery usually runs close to hilar bile duct carcinoma because of its anatomical situation, and the left hepatic artery runs far from the common bile duct and hilar bile duct confluence. The second advantage is that the right hepatic bile duct ramifies into multiple intrahepatic bile ducts immediately after the common bile duct ramifies into the first-order bile duct branches; the right and left hepatic ducts. The third advantage is that the portal vein also ramifies into the second-order branches immediately from the first-order branch of the portal vein at the right side. The fourth advantage is that the right-side caudate lobe, especially the paracaval portion cannot easily be discriminated from the right hepatic lobe, but the left-sided caudate lobe; namely, the Spiegel lobe, can be easily identified and removed from the left hepatic lobe. Therefore, it has been advocated that right-sided hepatectomy should be selected for radical resection for hilar cholangiocarcinoma to obtain a curative resection. However, some patients with advanced hilar cholangiocarcinoma mainly extensively involving the left hepatic duct and/or involving the left portal vein and the left hepatic artery cannot undergo right-sided hepatectomy. These patients have to be candidates for left-sided hepatectomy if surgical resection is to be achieved. Therefore, left-sided hepatectomy should be regarded more importantly as an option of surgical strategy for hilar cholangiocarcinoma. We have recently reported the usefulness of left-sided hepatectomy in the surgical treatment of hilar cholangiocarcinoma, although a curative surgical margin at the hepatic bile duct stump could not be obtained as easily as in right-sided hepatectomy [17].

The postoperative complication rates after surgical resections for hilar cholangiocarcinoma have been reported to be still high even after surgical techniques and perioperative management have improved so much. However, as reported, surgical mortality rates may be decreasing gradually at most high-volume centers. In the present series during the period between January 2001 and December 2008, the surgical mortality rate was 1.9%. This mortality rate is clearly decreasing as compared to the rate previously reported by us. However, for patients with hilar cholangiocarcinoma and obstructive jaundice, major extended hepatectomy should still be carefully performed in selected patients as it causes major surgical stress to the patients.

In conclusion, the surgical strategy for hilar cholangiocarcinoma has been improved remarkably, and major surgical hepatectomy could be done with relative safety, and the aggressive surgical approaches including combined vascular resection may be justified for the surgical treatment of hilar cholangiocarcinoma. However, the adoption of new innovative therapeutic approaches might be required for further improvement of surgical outcome of hilar cholangiocarcinoma.

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TOPICS Current issues in mucin-producing tumor of the bile duct

Surgical strategy for mucin-producing bile duct tumor

Masayuki Ohtsuka · Fumio Kimura · Hiroaki Shimizu · Hiroyuki Yoshidome · Atsushi Kato · Hideyuki Yoshitomi · Katsunori Furukawa · Noboru Mitsuhashi · Dan Takeuchi · Tsukasa Takayashiki · Kosuke Suda · Masaru Miyazaki

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Abstract Tumors with copious mucin production within the intra- or extrahepatic bile ducts have been reported as mucin-producing bile duct tumors (MPBTs). Because mucin produced by these tumors causes recurrent cholangitis and obstructive jaundice, surgical resection should be indicated even if these tumors are regarded as benign. In order to choose the appropriate surgical procedure, exact preoperative assessment of tumor location and cancer extension is important, especially evaluation of the extent of superficial spreading through cholangioscopic observation and biopsy. In principle, MPBTs should be resected in a manner similar to that employed for other types of bile duct carcinomas. That is, major hepatectomy with or without extrahepatic bile duct resection or pancreaticoduodenectomy should be chosen as the surgical procedure, and intraoperative frozen section at the stumps of the bile duct is essential. On the other hand, when precise diagnosis is completed preoperatively and the lesion is diagnosed as adenoma or carcinoma with invasion confined to the ductal wall and limited superficial spreading, limited resections preserving organ functions as much as possible can be considered as a choice among surgical procedures. All ten patients with MPBT resected at our institution according to these strategies are still alive without tumor recurrence, with a median survival of 48.0 months.

Keywords Surgical resection · Mucin-producing bile duct tumor · Superficial spreading · Intraductal papillary mucinous neoplasm

Introduction

Most tumors arising from the intra- or extrahepatic bile ducts have the capacity to produce mucin, which is retained in the tumor cells in most cases. However, some tumors produce copious mucin within the intra- or extrahepatic bile ducts, resulting in obstructive jaundice and cholangitis, as well as marked dilatation of the bile ducts. These tumors have been reported as mucin-producing bile duct tumors (MPBTs).

Recently, it has been demonstrated that such MPBTs have a striking similarity to intraductal papillary mucinous neoplasms (IPMNs) of the pancreas [1–4], which are now a well-accepted clinical and pathological entity. Both types of tumors are characterized by predominantly polypoid or, rarely, flat growth and mucin production macroscopically; and, microscopically they are characterized by papillary fronds with fine vascular cores. Neoplastic epithelial cells in both types of tumors can be of pancreatobiliary type or they can show gastric or intestinal differentiation [4–6], and display a spectrum of cytoarchitectural atypia ranging from none to borderline to marked; they can also be associated with invasive carcinoma [5]. MPBTs are regarded as a biliary counterpart of IPMNs of the pancreas, and the nomenclature "intraductal papillary neoplasm of the bile duct" has been proposed [6]. Some cases of biliary cystadenomas and cystadenocarcinomas might be also included in the category of MPBTs, but these tumors, especially those with ovarian-like stroma, should be excluded from the category of MPBT because of the different disease concepts underlying these categories [7].

M. Ohtsuka · F. Kimura · H. Shimizu · H. Yoshidome · A. Kato · H. Yoshitomi · K. Furukawa · N. Mitsuhashi · D. Takeuchi · T. Takayashiki · K. Suda · M. Miyazaki (✉)
Department of General Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuoh-ku, Chiba 260-8670, Japan
e-mail: masaru@faculty.chiba-u.jp

Similar to IPMNs of the pancreas, MPBTs have been considered to have relatively favorable prognoses after complete surgical resection. However, an appropriate surgical strategy has not ever been documented, partly because MPBT is an uncommon disease. Here, we describe our current surgical strategy for MPBTs, based on the modes of spread of these tumors.

Clinicopathologic features and modes of spread

One of the features of MPBTs is intraductal papillary growth. The papillary structure generally shows a visible polypoid lesion (Fig. 1a), while sometimes, papillary epithelial cells without a gross mass are confirmed only by microscopic examinations. In the latter case, only granular mucosa is observed macroscopically in the dilated bile ducts (Fig. 1b), or, in some cases, no distinct mucosal change is identified. Microscopically, similar to IPMNs of the pancreas, MPBTs often show varying degrees (carcinoma, borderline, and adenoma) of cytoarchitectural atypia, although the frequency of carcinoma is higher compared with that in IPMNs of the pancreas. In addition, MPBT sometimes has multiple lesions. Taoka et al. [8] reported a case of MPBT with four independent lesions.

A less invasive characteristic compared with other types of bile duct carcinomas may be another feature of MPBTs. In our experience with ten MPBTs, all but one of the carcinomas were in situ carcinoma or minimally invasive carcinoma confined to the ductal wall (Table 1). These observations can be partly attributed to the possible early detection of MPBTs due to excessive mucin that causes cholangitis and obstructive jaundice. However, patients with mucin-producing bile duct in situ carcinoma were reported to be often afflicted with the symptoms related to cholangitis for a long time before the diagnosis [9, 10], and, furthermore, recurrence more than 5 years after surgical resection of MPBTs was also experienced [9]. These facts suggest that MPBTs might be relatively slow-growing tumors.

MPBTs are often associated with superficial spreading along the mucosa of the bile duct. This mode of spread was seen in three cases (30%) in our series (Table 1). On the other hand, extramucosal spread is rarely observed in MPBTs, partly because of its less invasive characteristics, as mentioned above, although an extramucosal spreading pattern is frequently observed in other types of bile duct carcinomas [11].

Generally, lymph node metastasis or neural invasion is not experienced in MPBTs in which the depth of invasion is confined to the ductal wall. In fact, no MPBTs in our series had lymph node involvement (Table 1) or neural invasion. In contrast, MPBTs invading beyond the ductal wall seem to be associated with lymph node metastasis or neural invasion with almost the same frequency as that seen in other types of bile duct carcinomas [9, 12].

Remote metastases are rare in patients with MPBT. Besides hepatic and splenic recurrence after surgical resection [12], tumor seeding in the sinus tract of percutaneous transhepatic biliary drainage (PTBD) has been reported to be a characteristic recurrence site in this tumor [9].

Operative indication

Unlike patients with IPMNs of the pancreas, all patients with MPBTs should be treated, even if these tumors are regarded as benign, because mucin produced by MPBTs causes recurrent cholangitis and obstructive jaundice. Because no treatment option other than surgical resection

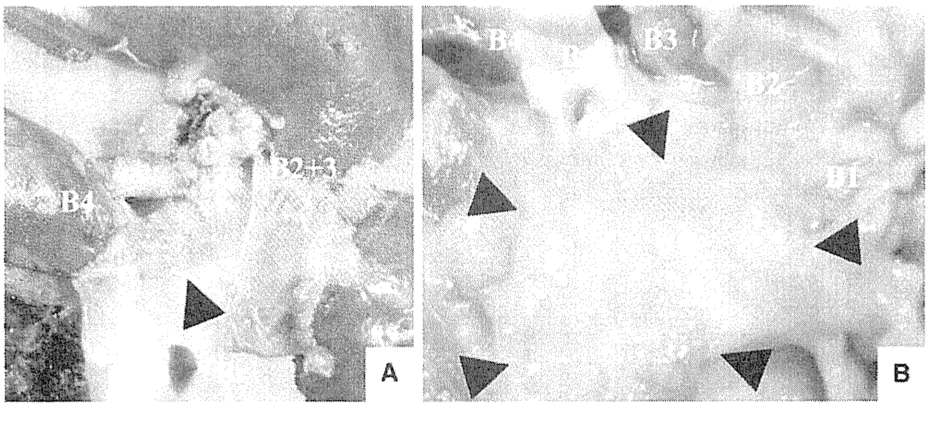

Fig. 1 Representative macroscopic findings of mucin-producing bile duct tumor. **a** Well-demarcated elevated polypoid mass was identified in the lumen of the left hepatic duct (*arrowhead*). **b** Only granular and small papillary mucosa were observed (*arrowheads*). *B4* Medial segmental bile duct; *B2* left lateral posterior segmental bile duct; *B3* left lateral anterior segmental bile duct; *B1* caudate lobe bile duct; *Br* right hepatic duct

Table 1 Characteristics of patients with mucin-producing bile duct tumors (MPBTs)

Age (years)/gender	Surgical procedure	Location	Depth of invasion	Superficial spreading	Lymph node metastasis	Outcome (no. of months)
65/M	Left hemihepatectomy+S1	B3	Invasive (confined to the ductal wall)	No	No	Alive without recurrence (40)
49/M	Extended left hemihepatectomy+S1+BDR	B2	Invasive (confined to the ductal wall)	No	No	Alive without recurrence (76)
77/F	Left hemihepatectomy+S1+BDR	B3	Invasive (confined to the ductal wall)	No	No	Alive without recurrence (51)
73/F	Right hemihepatectomy+BDR	B8	Invasive (confined to the ductal wall)	Yes	No	Alive without recurrence (61)
61/M	Extensive hilar BDR	Hilar	Noninvasive	No	No	Alive without recurrence (38)
69/M	Extended left hemihepatectomy+S1+BDR	Bl	Noninvasive	No	No	Alive without recurrence (50)
70/M	Left trisegmentectomy+BDR	Hilar	Invasive (confined to the ductal wall)	Yes	No	Alive without recurrence (71)
53/M	S1+BDR	Bm	Invasive (confined to the ductal wall)	No	No	Alive without recurrence (54)
66/M	Extended left hemihepatectomy+BDR	Bl	Noninvasive	Yes	No	Alive without recurrence (30)
60/M	Left hemihepatectomy+S1	B3	Invasive (beyond the ductal wall)	No	No	Alive without recurrence (9)

S1 caudate lobectomy, *BDR* bile duct resection, *B3* left lateral anterior segmental bile duct, *B2* left lateral posterior segmental bile duct, *B8* right anterior superior segmental bile duct, *Bl* left hepatic duct, *Bm* middle portion of the extrahepatic bile duct

has been established to date, all MPBTs are recommended to be surgically resected as long as the patient is a good surgical candidate with a reasonable life expectancy.

Surgical procedures

In order to choose the appropriate surgical procedure, exact preoperative assessment of tumor location and cancer extension is important, because complete resection of MPBTs is expected to provide a better prognosis than that experienced with other types of bile duct carcinomas. In particular, for evaluating of the extent of superficial spreading, cholangioscopic observation and biopsy after sufficient mucin drainage seems to be essential. These approaches can also be of aid in the diagnosis of the degree of cytoarchitectural atypia within the main tumor. However, assessment of invasion depth is not always easy unless MPBTs have invaded the hepatic parenchyma or large vessels such as the portal vein and hepatic artery, although intraductal ultrasonography may be useful for this assessment.

On the basis of these preoperative assessments, the extent of hepatic resection and the point where the bile duct is to be divided should be planned. In principle, MPBTs should be resected in a manner similar to that employed for other types of bile duct carcinomas. That is, major hepatectomy with or without extrahepatic bile duct resection (BDR) or pancreaticoduodenectomy should be chosen as the surgical procedure. Intraoperative frozen section at the stumps of the bile duct is essential to confirm a cancer-free surgical margin. Even it is suspected that the tumor is an adenoma, a similar strategy should be considered, because MPBTs are often composed of varying degrees of cytoarchitectural atypia, and an accurate diagnosis of the maximum degree of cytoarchitectural atypia cannot be always made by preoperative biopsy. In fact, two MPBTs in our series, which were finally diagnosed as cancer, were preoperatively assessed as borderline malignancy and adenoma. Whenever the tumor is suspected to be a cancer, especially if it has invaded beyond the ductal wall, lymph node dissection should be performed. In our series, six patients underwent more than hemihepatectomy with extrahepatic BDR and two had hemihepatectomy with caudate lobectomy.

On the other hand, when precise diagnosis is completed preoperatively and the lesion is diagnosed as an adenoma or carcinoma with invasion confined to the ductal wall and limited superficial spreading, limited resections preserving organ functions as much as possible can be considered as a choice among surgical procedures, although these should always be contingent on a careful intraoperative final assessment. We experienced a case in which extensive

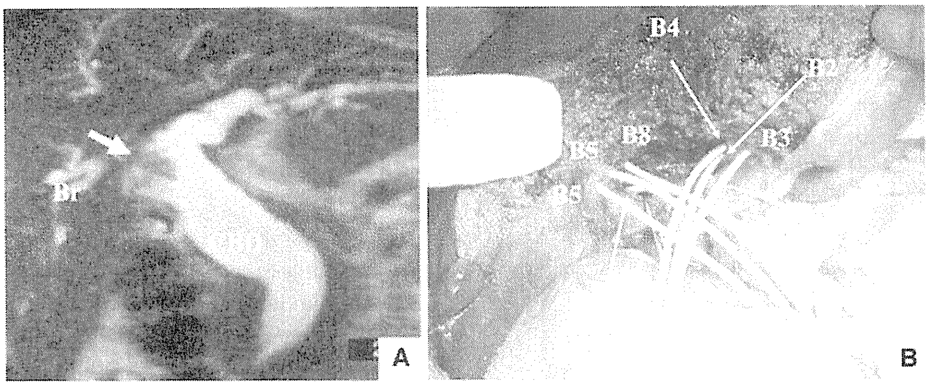

Fig. 2 Mucin-producing bile duct tumor. **a** Magnetic resonance cholangiopancreatography reveals a polypoid mass within the hilar portion of the bile duct (*arrow*). *Br* Right hepatic duct; *Bl* left hepatic duct; *CBD* common bile duct. **b** Intraoperative findings. Tumor was resected by extensive hilar bile duct resection, using a transhepatic approach. *B2* Left lateral posterior segmental bile duct; *B3* left lateral anterior segmental bile duct; *B4* medial segmental bile duct; *B5* right anterior inferior segmental bile duct; *B6* right posterior inferior segmental bile duct; *B7* right posterior superior segmental bile duct; *B8* right anterior superior segmental bile duct

hilar BDR, using a transhepatic approach, [13] was performed in a patient with an MPBT that originated from the hilar bile duct (Fig. 2). This tumor was preoperatively diagnosed as borderline malignancy or in situ carcinoma, by the use of several diagnostic modalities including cholangioscopy and intraductal ultrasonography. Consequently, curative resection was successfully achieved without performing combined major hepatectomy. This patient is still alive without disease recurrence at 38 months after the operation.

Several authors have recommended that combined resection of the PTBD sinus tract or ethanol injection into the sinus tract should be performed during the definitive surgery [9, 14, 15], because tumor seeding is sometimes encountered in the sinus tract of PTBD. Sakamoto et al. [9] have shown that 1 of 11 patients with MPBTs developed a seeding tumor at the previous PTBD sinus tract 17 months after definitive surgery.

Surgical outcome

Previous reports have shown that complete resection provides a better prognosis in patients with MPBT than in those with other types of bile duct carcinomas. Chen et al. [16] reported that the 1-, 3-, and 5-year survival rates after surgical resection for 22 MPBT patients were 86.5, 59.0, and 31.0%, respectively, rates that were significantly better than those for 148 patients with other types of bile duct carcinomas. Similarly, Sakamoto et al. [9] showed that 7 of their 11 patients with MPBT survived for 5 years after surgery, and 4 patients survived for 10 years. In our series, all ten patients with MPBT are still alive without tumor recurrence after surgical resection, with a median survival of 48.0 months (Table 1).

Although, biologically, MPBTs appear to show low aggressiveness and are slowly progressive, the apparently better prognosis in MPBTs compared with that of other types of bile duct carcinomas may be partly attributable to the high prevalence of early-stage tumors. In most patients with MPBTs, the depth of invasion is minimal, while in most patients with other types of bile duct carcinomas, the depth of invasion is beyond the ductal wall. Once MPBTs invade beyond the ductal wall, lymph node metastasis and invasion into adjacent organs such as the stomach and the pericardium occurs, and the outcome in these patients is not always favorable. Hirota et al. [12] have reported a case in which the cancer, initially with lymph node metastasis, recurred in the liver and spleen 24 months after surgical resection. Sakamoto et al. [9] have also reported that a patient with invasive MPBT died 6 months after surgical resection. Therefore, similar to cases of IPMN of the pancreas, it is currently not clear whether an invasive cancer derived from in situ MPBT has a better prognosis than the more common bile duct carcinoma. In this regard, further observation with a larger number of cases is required.

Follow up

Few reports have described the recurrence of MPBTs after surgical resection [1, 9, 12]. Local, peritoneal, and hepatic recurrences have been observed in patients with MPBT invading beyond the ductal wall. In addition, Lee et al. [17] have reported that two patients with biliary papillomatosis, which is the same disease entity as MPBT when these tumors produce excessive mucin, had disease recurrence at the surgical margin and the residual intrahepatic bile ducts, despite an initial negative surgical margin. Because some

MPBTs have been shown to be multifocal [8], it is possible that recurrence in the remaining bile ducts may develop after apparently complete resection of even noninvasive tumors. Therefore, patients with MPBT, even if it is noninvasive, should undergo careful follow up and surveillance to monitor for the development of recurrent disease. Furthermore, long-term follow up appears to be necessary particularly when cancer cells are observed at the stump of the bile duct through superficial spreading, because carcinoma in situ at the stump of the bile duct could cause late recurrence after surgery [18].

Conclusions

Previous reports have suggested that most cases of MPBT were at a relatively early stage at diagnosis. Therefore, a favorable outcome would be expected with the appropriate surgical resection, on the basis of precise preoperative assessment.

However, because it is only recently that MPBT has been proposed as a new disease category, there are several controversies that should be solved. It is not clear whether MPBT and biliary intraductal tumor without extracellular intraductal mucin production belong to a single tumor entity, as proposed by Zen et al. [6]. Differences in carcinogenesis between MPBT and other types of bile duct carcinomas have not been fully clarified [19]. Controversy still also remains over the surgical strategy. Follow up has been limited in previous series, and management of positive tumor margins of the bile duct stump was not standardized. Because the relative risk and significance of the varying degrees of cytoarchitectural atypia of MPBTs have not yet been fully established, management decision-making (whether or not further resection should be performed) is difficult when adenoma or borderline atypia exists at the stump of the bile duct. In regard to these issues, which are also still controversial in IPMNs of the pancreas [20], further investigations are needed in a large number of cases.

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Risk factors of liver dysfunction after extended hepatic resection in biliary tract malignancies

Kosuke Suda, M.D., Ph.D., Masayuki Ohtsuka, M.D., Ph.D.*, Satoshi Ambiru, M.D., Ph.D., Fumio Kimura, M.D., Ph.D., Hiroaki Shimizu, M.D., Ph.D., Hiroyuki Yoshidome, M.D., Ph.D., Masaru Miyazaki, M.D., Ph.D.

Department of General Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuoh-ku, Chiba 260-8670, Japan

KEYWORDS:
Biliary tract malignancies;
Extended hepatectomy;
Postoperative hyperbilirubinemia;
Remnant liver volume/entire liver volume ratio;
Indocyanine green retention rate at 15 minutes

Abstract

BACKGROUND: Postoperative hepatic insufficiency is a critical complication after extended hepatic resection in patients with biliary tract malignancies, the majority of whom suffer from obstructive jaundice. The aim of this study was to assess clinical parameters linked to this type of liver dysfunction.

METHODS: A total of 111 patients were retrospectively reviewed. Patient background, pre- and intraoperative parameters, and a ratio of remnant liver volume/entire liver volume (RLV/ELV) as a volumetric parameter were compared between patients with and without postoperative hyperbilirubinemia and subsequent fatal outcome.

RESULTS: Logistic regression indicated that only RLV/ELV ratio was an independent factor influencing postoperative hyperbilirubinemia, and RLV/ELV ratio and indocyanine green retention rate at 15 minutes (ICG-R15) were factors affecting survival. Patients with RLV/ELV less than 40% had 7.6 times the risk of postoperative hyperbilirubinemia, while no patients with RLV/ELV greater than 40% and ICG-R15 less than 25% died of liver failure.

CONCLUSIONS: The RLV/ELV ratio was the factor with the greatest impact on liver dysfunction after extended hepatectomy in patients with biliary tract malignancies.

Recent reports have suggested that aggressive surgical approaches with extended hepatic resection may result in improved prognosis for patients with biliary tract malignancies, such as hilar cholangiocarcinoma, advanced gallbladder carcinoma, and intrahepatic cholangiocarcinoma.[1–7] With advances in anatomic knowledge of the liver and hepatic hilus, as well as in perioperative management and surgical techniques, the indications for these approaches have been expanded, and the likelihood of curative resection has increased. However, serious complications are sometimes encountered after surgery of this type. Postoperative hepatic insufficiency is one of the most serious complications, because it usually has a fatal outcome.

Many factors linked to postoperative hepatic dysfunction after extended hepatic resection have been reported, including preoperative liver function, remnant liver volume, and amount of blood loss during surgery.[8–13] These analyses have usually been performed in patients with hepatic metastasis[8,13] or hepatocellular carcinoma,[9–11] and few have

* Corresponding author. Tel.: +81-43-226-2103; fax: +81-43-226-2552.
E-mail address: otsuka-m@umin.ac.jp
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examined these factors in patients with biliary tract malignancies, the majority of whom suffer from obstructive jaundice.[14] Obstructive jaundice is known to be an important risk factor for postoperative liver failure after extended hepatic resection, and, in fact, unexpected liver dysfunction is sometimes experienced after such operations. It may be attributed in such cases to impaired hepatic functional reserve due to chronic cholestasis. Therefore, preoperative biliary drainage is generally provided for such patients, to restore liver function before extended hepatic resection, although its impact on postoperative liver dysfunction remains controversial.

In this study, we analyze various pre- and intraoperative factors to identify patients at risk of developing postoperative liver dysfunction, by reviewing a single-institution study of patients with biliary tract malignancies, especially focused on patients undergoing extended hepatic resection.

Patients and Methods

Patients

Between December 1981 and March 2005, a total of 111 patients with biliary tract malignancies underwent extended hepatic resection at Chiba University Hospital. Extended hepatic resection was defined as resection of more than 3 Couinaud segments, that is, extended hemihepatectomy or trisegmentectomy.

The patients were 43 women and 68 men with a mean age of 66.1 years (range 40–83) at the time of surgery. The indications for resection were hilar cholangiocarcinoma in 59 patients, gallbladder carcinoma in 29, and intrahepatic cholangiocarcinoma in 23. Eight patients (7.4%) had chronic viral hepatitis but not cirrhosis, and 69 patients (63%) developed obstructive jaundice with serum total bilirubin levels exceeding 3 mg/dL on admission (range 3.1–38.0 mg/dL). All patients with obstructive jaundice received percutaneous transhepatic or endoscopic biliary drainage preoperatively to relieve cholestasis. Hepatic resection was performed principally after total bilirubin concentration had declined below 3 mg/dL, although 13 patients (19%) still had jaundice at the time of surgery (3.1–5.8 mg/dL) because their jaundice could not be expected to be relieved any longer. The period from insertion of the drainage tube to surgery ranged from 7 to 96 days (mean 45.1). Portal vein embolization was provided prior to hepatic resection for 36 patients (32%). This procedure was introduced to our institution in August 1994. During the study period a total of 42 patients were considered for this approach. However, 6 of these 42 patients did not have hepatic resection, because of peritoneal dissemination (1 patient) or irresectable disease at the laparotomy (2 patients), the revelation of distant metastasis after portal vein embolization (1 patient), failure to relieve jaundice even after biliary drainage (1 patient), and failure to improve calculated future liver remnant volume sufficiently (1 patient). Surgical procedures are listed in Table 1. Bilioenteric anastomosis was performed in 108 patients.

Postoperative liver dysfunction

Postoperative liver dysfunction after extended hepatic resection was assessed in terms of postoperative hyperbilirubinemia and subsequent fatal outcome. Postoperative hyperbilirubinemia was defined as an increase in serum total bilirubin greater than 10 mg/dL, without a hemolytic or obstructive mechanism, within 2 weeks after surgery.

Perioperative parameters

To analyze risk factors for developing postoperative liver dysfunction, the following parameters were assessed: (1) patient background and preoperative parameters, including

Table 1 Types of operative procedures

	Hilar cholangiocarcinoma (n = 59)	Gallbladder carcinoma (n = 29)	Intrahepatic cholangiocarcinoma (n = 23)
Type of hepatic resection			
Extended right hemihepatectomy	28	24	8
Extended left hemihepatectomy	25	5	11
Right trisegmentectomy			3
Left trisegmentectomy	6		1
Associated procedure			
Bile duct resection and reconstruction	59	29	20
Partial resection of colon		3	
Partial resection of duodenum	1	1	
Vascular resection & reconstruction			
Portal vein	15	6	6
Inferior vena cava			5
Hepatic artery	3	1	1

sex, age, presence of chronic viral hepatitis, presence of obstructive jaundice, serum total bilirubin levels at the time of surgery, the rate of decrease in the level of serum bilirubin ("b value"), hepatic functional reserve tests, preoperative portal vein embolization, and presence of cholangitis before operation; (2) intraoperative parameters, including type of hepatic resection, combined vascular resection and reconstruction, bilioenteric anastomosis, amount of blood loss during surgery, operative time, and total duration of intermittent Pringle maneuver; and (3) volumetric parameters, including ratio of remnant liver volume/entire liver volume (RLV/ELV).

As reported by Shimizu et al,[15] the b value was calculated by the nonlinear least squares method, fitted to the equation $y = ae^{bx}$, where y is the serum total bilirubin level, x is the number of days after drainage, a is represented bilirubin levels on the drainage day, b is the rate of decrease of serum bilirubin, and e is the base of the natural logarithm. Based on these data, we categorized the patients into 3 groups: patients with rapid bilirubin decrease ($b < -.05$), patients with slow bilirubin decrease ($b > -.05$), and patients without obstructive jaundice (b value not available). As hepatic functional reserve tests, both indocyanine green (ICG) clearance test and the galactose tolerance test (GaTT) were performed. The ICG clearance test, by means of a single intravenous injection of ICG .5 mg/kg, was estimated as a serum retention rate at 15 minutes after injection (ICG-R15). On the GaTT, a half-life of serum galactose concentration (GaTT-T/2) was determined after an intravenous injection of 100 mL of D-galactose. These tests were performed just before surgery. Portal vein embolization was provided when extended right hemihepatectomy, or right or left hepatic trisegmentectomy, were planned and the measured future liver remnant volume was expected to be less than 40% of the entire liver volume. This policy was not changed throughout the period since the introduction of this approach. Preoperative cholangitis, occurring within a week before surgery, was diagnosed by means of clinical and hematological findings. When cholangitis had subsided, as a result of antibiotic administration, cholangitis was classified as mild, and when the insertion of an additional drainage tube was required, cholangitis was judged as severe.

For a volumetric analysis, preoperative computed tomography scan images were retrospectively used to calculate the volume of the entire liver and the resected liver. To summarize, serial transverse scans were performed at .8-cm intervals, to include the entire liver, after intravenous bolus injection of contrast medium. The total liver, excluding tumor, was outlined on each slice, and the sum of the slices was calculated by means of integrated software techniques, using density threshold. This was repeated for volume of liver resected. The difference between ELV and volume of liver resected was considered RLV. In patients who underwent portal vein embolization, this analysis was performed just before surgery, since the RLV/ELV ratio was significantly improved after portal vein embolization (Table 2).

Table 2 Liver volume before and after portal vein embolization

	Portal vein embolization		
	Before	After	*P* value
RLV/ELV (%)	33.4 ± 6.5	41.7 ± 6.7	<.0001

RLV = remnant liver volume; ELV = entire liver volume.

Statistics

Logistic regression was performed to identify possible risk factors of postoperative hyperbilirubinemia and subsequent fatal outcome associated with extended hepatic resection in cases of biliary tract malignancies. To reduce the number of variables considered in the model, univariate analysis was initially performed using Mann-Whitney test for continuous variables, and 2-tailed Fisher exact probability test or chi-square test for categorical variables. Only variables with $P < .05$ were considered for the model. Once these potential risk factors were identified, a backward stepwise procedure was used to establish the final model; the odds ratio and 95% confident interval were determined. Statistical calculations were performed using SPSS 13.0 program (SPSS Inc, Chicago, IL).

Results

Postoperative outcome

Seventeen of 111 patients (15.3%) with biliary tract malignancies who had extended hepatic resection developed postoperative hyperbilirubinemia. Of these patients, 9 (8.1%) died as a result of subsequent hepatic failure.

Patient background and preoperative parameters and postoperative outcome

Univariate analysis showed no significant risk factors for postoperative outcome in regard to patient background. Among preoperative parameters, only ICG-R15 was a significant factor for death due to hepatic failure. Factors relating to obstructive jaundice, such as presence of obstructive jaundice, serum total bilirubin levels at the time of surgery, and rate of decrease in the level of serum bilirubin, were not associated with either postoperative hyperbilirubinemia or subsequent fatal outcome. Similarly, preoperative cholangitis did not affect postoperative outcome (Tables 3 and 4).