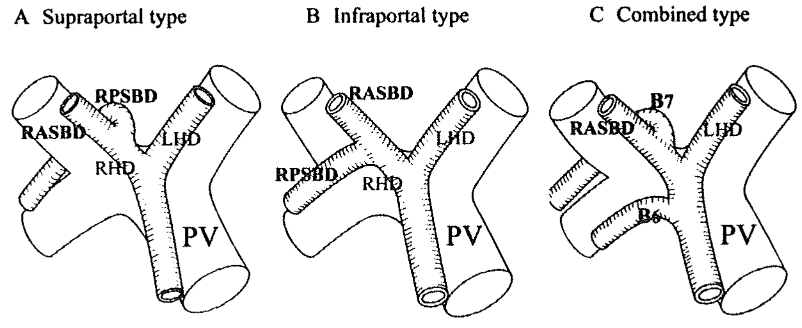


**FIGURE 1.** Confluence patterns of the right posterior sectional bile duct (RPSBD). (A); Supraportal type, the RPSBD runs cranially around the RPV to form a confluence with the right anterior sectional bile duct (RASBD) duct at cranial side of the RPV. (B); Infraportal type, the RPSBD runs caudal to the RPV and joins to the RASBD at caudal side of the RPV. (C); Combined type, there is no RPSBD. The ducts from segments 6 and 7 have separate confluences with the remaining biliary tree; one segmental duct runs in a supraportal position and the other in an infraportal position. Bl, left hepatic duct; Br, right hepatic duct; B6, segment 6 duct; B7, segment 7 duct; PV portal vein.

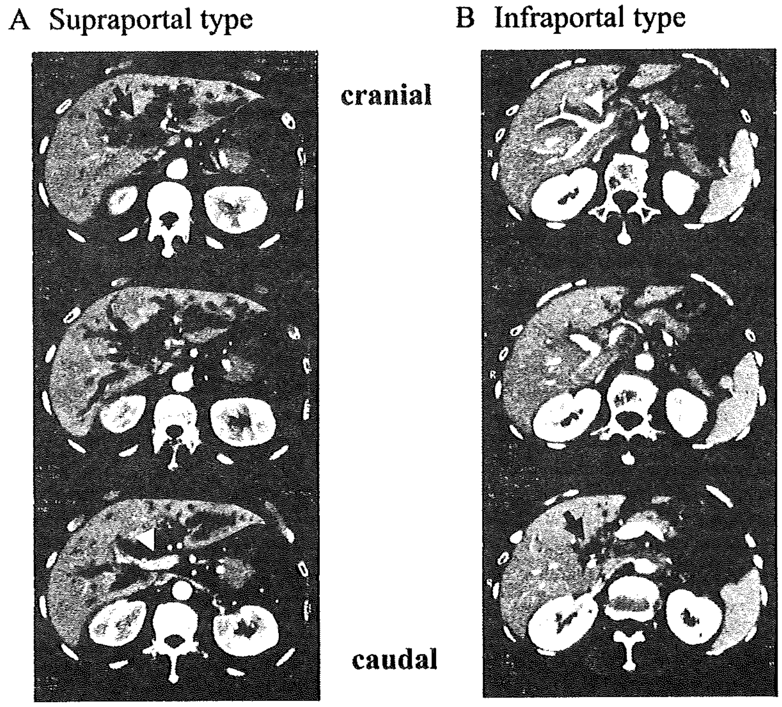


**FIGURE 2.** Diagnosis of the confluence pattern of the right posterior sectional bile duct (RPSBD) using contrast enhanced computed tomography. (A); Supraportal type, the RPSBD (arrow) joins to the distal bile duct at cranial side of the right portal vein (RPV) (arrowhead). (B); Infraportal type, the RPBD (arrow) joins to the distal bile duct at caudal side of the RPV (arrowhead).

In this study, we investigated confluence patterns of the RPSBD in relation to the right portal vein (RPV) in 67 patients who underwent LH extended to the hilar part of segment 5 and the entire segment 1 for hilar cholangiocarcinoma. Confluence patterns of the RPSBD was classified into the following 3 groups; (1) supraportal type: the RPSBD runs cranially around the RPV to form a confluence with the right anterior sectional bile duct (RASBD) at cranial side of the RPV (Fig. 1A), (2) infraportal type: the RPSBD runs caudal to the RPV and joins to the RASBD at caudal side of the RPV (Fig. 1B), and (3) combined type: there is no RPSBD. The ducts from segments 6 and 7 have separate confluences with the remaining biliary tree; one segmental duct runs in a supraportal position and the other in an infraportal position (Fig. 1C). Confluence patterns of the RPSBD were determined retrospectively by preoperative imaging studies, mainly contrast enhanced computed tomography (CT) or CT angiography (Fig. 2), and were confirmed by intraoperative observations based on the operative records, if available. In cases with marked biliary dilatation prior to biliary drainage (Fig. 2A), or with placement of biliary drainage catheter though the RPSBD, the course of the RPSBD in relation to the RPV can be easily determined by contrast enhanced CT. Meanwhile, although cholangiography does not enable a definitive diagnosis, the typical configuration of the RPSBD in the supraportal type, which is called Hjortsjo's Crook,[25] is a helpful clue (Fig. 3).

Patient background and preoperative parameters, including age, gender, indocyanine green retention rate at 15 min (ICG-R15), obstructive jaundice (presence/absence), and serum total bilirubin at the time of surgery were assessed. As intraoperative parameters, operative time, operative blood loss, number of bilioenteric anastomosis, combined pancreatoduodenectomy, and vascular resection and reconstruction were examined. Postoperative complications were also evaluated. Bilioenteric anastomotic leakage was diagnosed by cholangiographical demonstration of leak from the anastomosis via the biliary stent tube placed during surgery. On the other

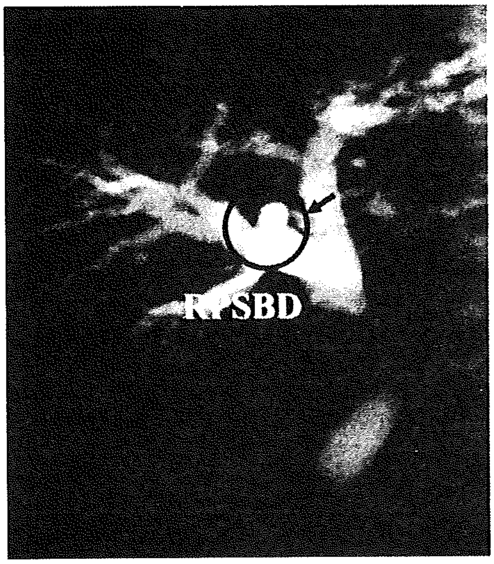

FIGURE 3. Cholangiography. The typical configuration of the right posterior sectional bile duct (RPSBD), which is called Hjortsjo's Crook (arrow), can be observed in the supraportal type.

hand, pathologic findings in resected specimens were evaluated using the TNM Classification of Malignant Tumors by the International Union Against Cancer (6th ed, 2002).

## Statistics

Results are expressed as the mean ± SD. Statistical analysis was performed using the $\chi^2$ test, and the Fisher exact test probability test, where appropriate. $P < 0.05$ was considered statistically significant. Overall survival curves were calculated using the Kaplan-Meier method, and log-rank test was used to determine significant differences in survival.

## RESULTS

In our series, curative resection was achieved in 41 patients out of 67 (61.2%) who had undergone LH extended to the hilar part of segment 5 and segment 1 for hilar cholangiocarcinoma, and the cumulative survival rates in patients with curative resection were significantly higher than the patients with noncurative resection, as shown in Figure 4. In these 67 patients, the confluence pattern of RPSBD could be reviewed retrospectively using imaging studies and operative records. However, definitive diagnosis was not possible in 4 cases because of incomplete imaging data. These cases were, therefore, excluded from this study. The remaining 63 cases were categorized as follows; 53 cases (84.1%) with the supraportal pattern, 8 cases (12.7%) with the infraportal pattern, and the remaining 2 cases (3.2%) with the combined pattern.

Patient characteristics are shown in Table 1. There were no significant differences between the groups in age, gender, ICG-R15 value, obstructive jaundice (presence/absence), and total bilirubin levels at time of operation. No significant differences in operative parameters such as the operative time, operative blood loss, number of the bilioenteric anastomosis, combined pancreatoduodenectomy, or combined vascular resection were found between the groups (Table 2). Histopathological findings in resected specimens are shown in Table 3. Histologic differentiation of tumors, lymph node involvement, and stage grouping based on International Union Against Cancer classification (6th edition) were not significantly different between the groups. On the other hand,

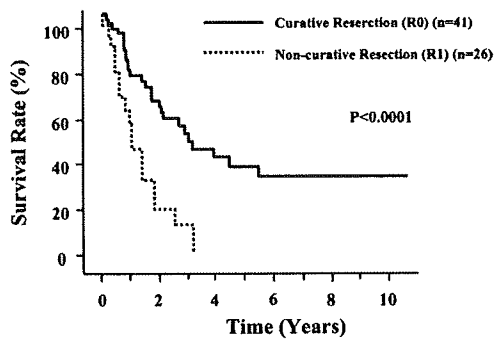


FIGURE 4. Patient survival rate according to curability after left hemihepatectomy extended to the hilar part of segment 5 and the entire segment 1 for hilar cholangiocarcinoma. The cumulative survival rates in patients (n = 41) with curative resection were significantly better than the patients (n = 26) with noncurative resection ($P < 0.0001$).

TABLE 1. Patient Characteristics

| | Supraportal Type | Infraportal Type | Combined Type |
|---|---|---|---|
| Number of the patient (%) | 53 (84.1) | 8 (12.7) | 2 (3.2) |
| Age (year) | 64.3 (41–73)* | 67.0 (40–73) | 60.5 (51–70) |
| Gender (men:women) | 4:1 | 6:2 | 2:0 |
| ICG-R15 (%) | 12.8 ± 8.9† | 13.0 ± 9.1 | 13.3 |
| Obstructive jaundice (−/+) | 5/48 | 1/7 | 0/2 |
| Total bilirubin at operation (mg/dl) | 1.8 ± 1.1 | 1.6 ± 1.0 | 1.8 |

*Mean (range).
†Mean ± SD.

TABLE 2. Operative Parameters

| | Supraportal Type (n = 53) | Infraportal Type (n = 8) | Combined Type (n = 2) |
|---|---|---|---|
| Operative time (min) | 515 ± 100* | 473 ± 21 | 523 |
| Operative blood loss (ml) | 1872 ± 1513 | 1676 ± 830 | 1250 |
| No. of bilioenteric anastomosis | 2.67 ± 0.72 | 2.33 ± 0.58 | 2.5 |
| Pancreatoduodenectomy (+/−) | 1/52 | 0/7 | 0/2 |
| Vascular resection (+/−) | 18:35 | 2:6 | 1:1 |
| Portal vein (+/−) | 16:37 | 2:6 | 1:1 |
| Hepatic artery (+/−) | 6:47 | 1:7 | 0:2 |

*Mean ± SD.

curative resection was possible in 6 cases (75.0%) in the infraportal group, which was better than that in the supaportal group, but the difference was not significant. Furthermore, positive margin at the proximal (hepatic) stump of the bile duct was not observed in any case of the infraportal group, but was observed in 20 cases out of 53 (37.7%) in the supraportal group, which was significantly different between these 2 groups.

**TABLE 3.** Histopathological Findings

| | Supraportal Type (n = 53) | Infraportal Type (n = 8) | Combined Type (n = 2) |
|---|---|---|---|
| Histological differentiation (G1/G2/G3)† | 18/25/10 | 2/4/2 | 1/1/0 |
| Lymph node metastasis (+/−) | 22/31 | 5/3 | 1/1 |
| Stage I/II/III/IV | 5/26/20/2 | 1/4/2/1 | 0/0/2/0 |
| Curability, n (%) | | | |
| Curative resection | 31 (58.5) | 6 (75.0) | 1 (50.0) |
| Non-curative resection | 22 (41.5) | 2 (25.0) | 1 (50.0) |
| Positive surgical margin | | | |
| Hepatic stump of the bile duct | 20 (37.7) | 0* (0) | 1 (50.0) |
| Duodenal stump of the bile duct | 6 (11.3) | 1 (12.5) | 1 (50.0) |
| Excisional surface | 10 (18.9) | 2 (25.0) | 0 (0) |

*$P < 0.05$ between supraportal type and infraportal type.
†According to UICC, 6th edition.

**TABLE 4.** Surgical Morbidity

| | Supraportal Type (n = 53) | Infraportal Type (n = 8) | Combined Type (n = 2) |
|---|---|---|---|
| Morbidity, n (%) | 23 (43.3) | 4 (50.0) | 1 (50.0) |
| Hyperbilirubinemia | 2 (3.7) | 1 (12.5) | 1 (50.0) |
| Sepsis | 2 (3.7) | 1 (12.5) | 0 (0) |
| Anastomosis leakage | 8 (15.1) | 0 (0) | 1 (50.0) |
| Pneumonia | 3 (5.7) | 0 (0) | 0 (0) |
| Pleural effusion | 10 (18.9) | 1 (12.5) | 0 (0) |
| Hepatic abscess | 3 (5.7) | 1 (12.5) | 0 (0) |
| Wound infection | 6 (11.3) | 1 (12.5) | 0 (0) |
| Ileus | 1 (1.9) | 1 (12.5) | 0 (0) |

Surgical morbidity is shown in Table 4. It was noted that bilioenteric anastomotic leakage occurred in 8 patients out of 53 (15.1%) in the supraportal group, but none in the infraportal group.

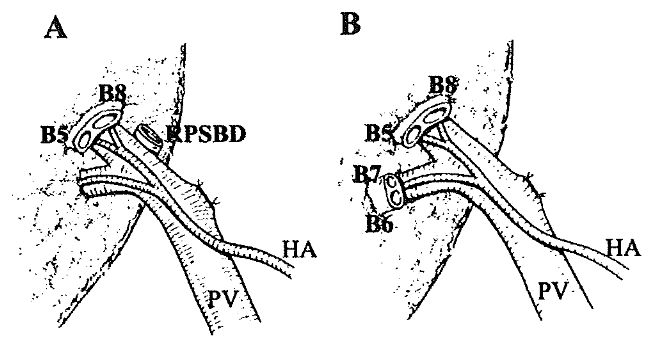


**FIGURE 5.** Stump of the right posterior sectional bile duct (RPSBD) after left hemihepatectomy extended to the hilar part of segment 5 and the entire segment 1. (A); Supraportal type, the stump of the RPSBD is posterior (dorsal) to the right portal vein (RPV). (B); Infraportal type, the stump of the RPSBD is anterior (ventral) side to the RPV. HA, hepatic artery; PV, portal vein; B5, segment 5 duct; B8, segment 8 duct; B6, segment 6 duct; B7, segment 7 duct.

## DISCUSSION

Hilar cholangiocarcinoma is a significant therapeutic challenge for biliary surgeons because only a surgical resection with tumor free margins is the most important factor for prolonged survival.[3–12] Accurate evaluation of longitudinal cancer extension is essential for achieving curative resection in patients with hilar cholangiocarcinoma. Detailed evaluation of biliary anatomy at hepatic hilus is also required to ensure negative ductal margin, especially in the case of LH. Anatomic variability of the sectional ramification is much higher in the right liver (remnant side after left-sided hepatectomy), and distance to the sectional ramification is also shorter than the left liver.[18] Recently, Ohkubo et al[26] have reported on detailed anatomic variations at the hepatic hilus using surgically resected specimens, concluding that precise recognition of anatomic variation is a crucial key to successful living donor liver transplantation.

In this study, we investigated confluence patterns of the RPSBD in relation to the RPV in patients with hilar cholangiocarcinoma applied to LH, and further evaluated their relation to the clinicopathological outcome. To our knowledge, this is the first study to examine the relationship between bilio-vascular anatomic variation and clinicopathological outcome in hilar cholangiocarcinoma. In our series, the frequency of the infraportal pattern of the RPSBD was 12.7% (8/63), which is similar to that in a previous report.[26] Surgical curability tended to be better in the infraportal group than in the supraportal group, but differences were not significant. Meanwhile, positive margin at the proximal stump of the bile duct in the infraportal group was significantly lower than in the supraportal group. In addition, incidence of bilioenteric anastomotic leakage was quite different between the groups. Anastomotic leakage occurred in 8 patients out of 53 (15.1%) in the supraportal group, but none (0/8) in the infraportal group, although operation time and number of bilioenteric anastomosis were similar between the groups. The stump of the RPSBD was a single orifice in all 53 cases in the supraportal group, and was posterior (dorsal) to the RPV after LH, which is the limit point of the RPBD division (Fig. 5A). Anastomosis of the RPSBD with the jejunum may be technically more difficult, because of the deep position and the posterior side of the RPV. On the other hand, the stump of the RPSBD in the infraportal type is anterior (ventral) side to the RPV (Fig. 5B). This anatomic position possibly enables more proximal resection of the

RPSBD, resulting in 2 orifices (segment 6 and 7 ducts) of the RPSBD in some cases, but these were easily grouped (duct-pasty) to form one anastomotic orifice. An accurate anastomosis with the jejunum is also more likely to be possible than in the case of the supraportal type.

In conclusion, the negative margin of the RPSBD and secure reconstruction could be more easily achieved in the infraportal group than in the supraportal group, due to the anatomic course of the RPSBD in relation to the RPV. Our study also suggests that left trisectionectomy might not be needed to achieve curative resection in some cases with an infraportal pattern of the RPSBD, even if the tumor infiltrates to the right secondary bile ducts. Since misunderstanding of the biliary anatomy at hepatic hilus in resectional surgery may easily lead to postoperative biliary complication,[27] preoperative recognition as well as intraoperaive understanding of the infraportal RPSBD is apparently important for safe and curative resection in patients with hilar cholangiocarcinoma. In addition, when left-sided hepatectomy is indicated in patients with Bismuth IIIb type tumor, diagnosis of the confluence patterns of the RPSBD in relation to the RPV may be clinically useful, and should be well-recognized by biliary surgeons.

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# 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 $\chi^2$ 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.

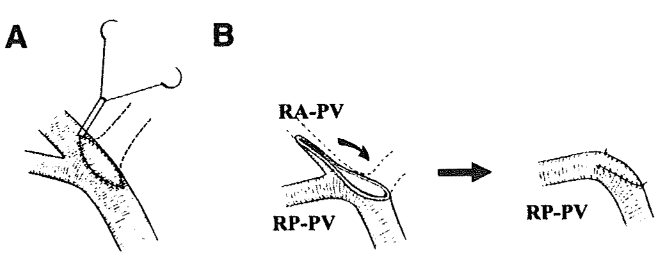


**FIGURE 1.** Methods of portal vein reconstruction after wedge resection of portal bifurcation after left-sided hepatectomy for hilar cholangiocarcinoma. A, Inferior mesenteric vein patch graft. B, Patch repair using right-side wall of the right anterior branch of the portal vein (RA-PV) in left trisectionectomy.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

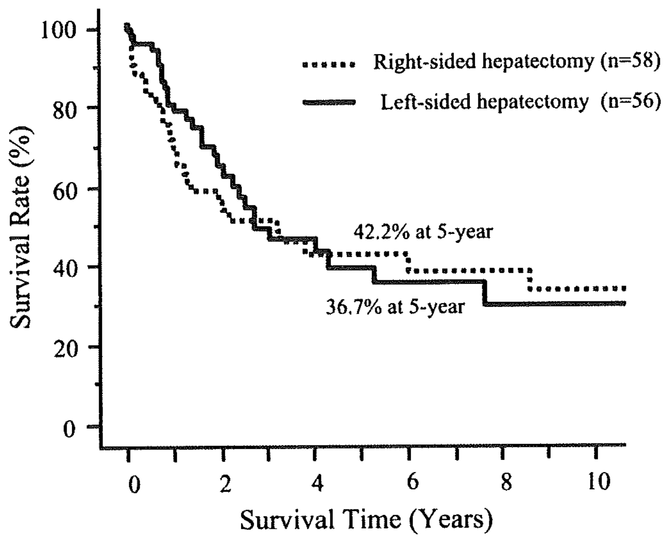


**FIGURE 2.** Survival curves after curative (R0) resection in patients undergoing right- or left-sided hepatectomy for hilar cholangiocarcinoma.

## 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

 

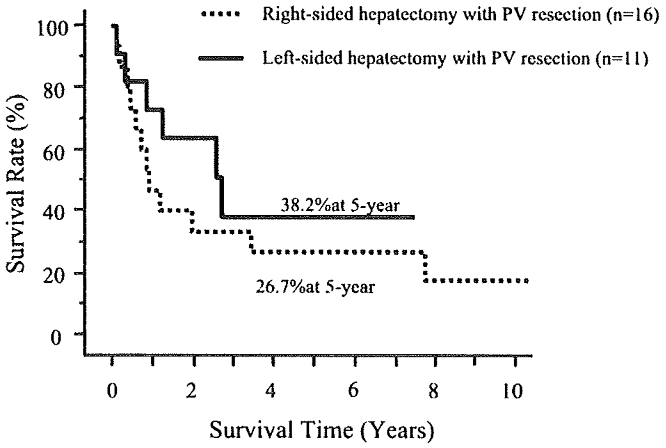


**FIGURE 3.** Survival curves after curative (R0) resection in patients undergoing right-sided hepatectomy with portal vein resection or left-sided hepatectomy with portal vein resection for hilar cholangiocarcinoma.

**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).

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

| | Survival Rate % (n) | | |
|---|---|---|---|
| Factors (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

| | | 95% Confidence Intervals | | |
|---|---|---|---|---|
| Factors | Relative Risk | 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.

## 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 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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# 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).

**Table 3** Risk factors for postoperative hyperbilirubinemia in patients with biliary tract malignancies

| Parameter | No postoperative hyperbilirubinemia (n = 94) | Postoperative hyperbilirubinemia (n = 17) | *P* value |
|---|---|---|---|
| Patient background and preoperative parameters | | | |
| Gender (M/F) | 58/36 | 10/7 | .82 |
| Age (y) | 66.2 ± 8.7 | 65.9 ± 8.6 | .89 |
| Chronic viral hepatitis (+) | 7 | 1 | .81 |
| Obstructive jaundice (+) | 56 | 12 | .75 |
| Serum total bilirubin level at operation (mg/dL) | 1.5 ± 1.1 | 2.0 ± 1.4 | .10 |
| b value (<−.05/>−.05) | 41/16 | 7/6 | .24 |
| ICG-R15 (%) | 12.4 ± 8.1 | 16.6 ± 9.8 | .07 |
| GaTT-T/2 (min) | 21.2 ± 7.4 | 22.7 ± 8.8 | .47 |
| Portal vein embolization (+) | 31 | 5 | .75 |
| Cholangitis (+) (mild/ severe) | 18/7 | 5/1 | .59 |
| Intraoperative parameters | | | |
| Type of hepatic resection (ELH/ERH/TS) | 38/49/7 | 3/11/3 | .15 |
| Vascular resection and reconstruction (+) | 27 | 7 | .30 |
| Bilioenteric anastomosis (+) | 91 | 17 | .46 |
| Blood loss during operation (mL) | 1,769 ± 1,959 | 4,438 ± 5,266 | .01 |
| Operative time (min) | 489 ± 96 | 562 ± 142 | .01 |
| Total duration of intermittent Pringle maneuver (min) | 36.2 ± 9.7 | 38.3 ± 17.6 | .54 |
| Volumetric parameter | | | |
| RLV/ELV (%) | 55.1 ± 16.9 | 42.4 ± 15.7 | .009 |

ELH = extended left hepatectomy; ERH = extended right hepatectomy; TS = trisegmentectomy; RLV = remnant liver volume; ELV = entire liver volume.

## Intraoperative parameters and postoperative outcome

The amount of blood loss during surgery and the operative time were significantly greater among patients who developed postoperative hyperbilirubinemia and who subsequently died than among those without postoperative liver dysfunction. Factors related to surgical procedures were not significantly associated with postoperative liver dysfunction (Tables 3 and 4).

**Table 4** Risk factors for postoperative mortality due to liver failure in patients with biliary tract malignancies

| Parameter | No postoperative fatal outcome (n = 102) | Postoperative fatal outcome (n = 9) | *P* value |
|---|---|---|---|
| Patient background and preoperative parameters | | | |
| Gender (M/F) | 64/38 | 4/5 | .28 |
| Age (y) | 65.8 ± 8.8 | 69.0 ± 6.0 | .29 |
| Chronic viral hepatitis (+) | 7 | 1 | .64 |
| Obstructive jaundice (+) | 62 | 6 | .81 |
| Serum total bilirubin level at operation (mg/dL) | 1.6 ± 1.2 | 1.8 ± 1.3 | .60 |
| b value (<−.05/>−.05) | 44/19 | 4/3 | .58 |
| ICG-R15 (%) | 12.4 ± 8.0 | 19.6 ± 11.2 | .02 |
| GaTT-T/2 (min) | 21.4 ± 4.2 | 21.9 ± 9.8 | .98 |
| Portal vein embolization (+) | 33 | 3 | .81 |
| Cholangitis (+) (mild/ severe) | 19/7 | 4/1 | .16 |
| Intraoperative parameters | | | |
| Type of hepatic resection (ELH/ ERH/ TS) | 41/53/8 | 0/7/2 | .92 |
| Vascular resection and reconstruction (+) | 30 | 4 | .35 |
| Bilioenteric anastomosis (+) | 99 | 9 | .60 |
| Blood loss during operation (mL) | 1,942 ± 2,126 | 4,848 ± 6,862 | .03 |
| Operative time (min) | 494 ± 100 | 573 ± 160 | .04 |
| Total duration of intermittent Pringle maneuver (min) | 36.2 ± 14.1 | 4.3 ± 2.4 | .76 |
| Volumetric parameter | | | |
| RLV/ELV (%) | 54.8 ± 16.9 | 35.1 ± 1.7 | .004 |

ELH = extended left hepatectomy; ERH = extended right hepatectomy; TS = trisegmentectomy; RLV = remnant liver volume; ELV = entire liver volume.

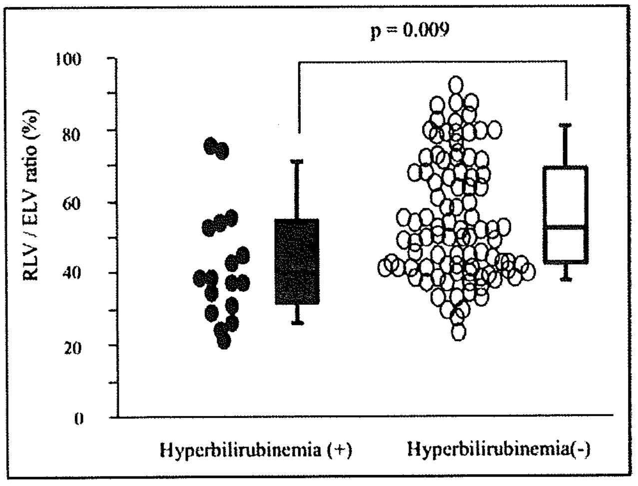


**Figure 1** A comparison of the RLV/ELV ratios of patients with and without postoperative hyperbilirubinemia. Mean RLV/ELV ratio in patients with hyperbilirubinemia was 42.4% ± 15%, while that in patients without hyperbilirubinemia was 55.1% ± 17%. The RLV/ELV ratio in patients with postoperative hyperbilirubinemia was significantly lower than in patients without hyperbilirubinemia (p = 0.009).

## Volumetric analysis and postoperative outcome

The RLV/ELV ratio was significantly lower in patients with postoperative liver dysfunction than in patients without postoperative liver dysfunction ($P < .01$). Mean RLV/ELV ratio in patients with postoperative hyperbilirubinemia was 42.4% ± 15 %, while that in patients without postoperative hyperbilirubinemia was 55.1% ± 17 % (Figure 1). Patients who ultimately died of liver failure had the lowest RLV/ELV ratios, with a mean of 35.1% ± 11%. Peak postoperative serum total bilirubin levels were negatively correlated with RLV/ELV ratio (Figure 2) (Tables 3 and 4).

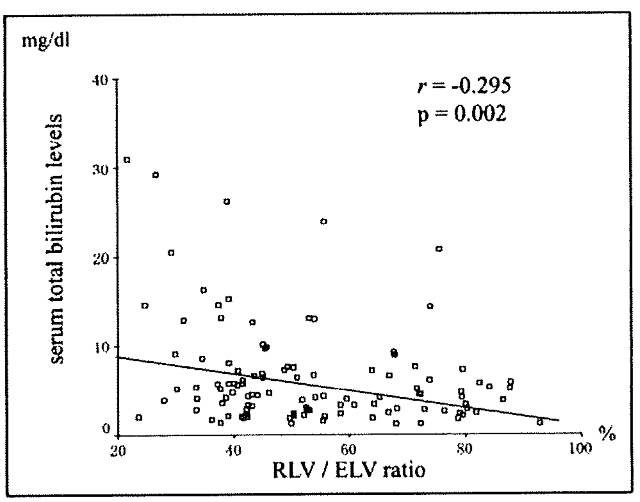


**Figure 2** Relationship between RLV/ELV ratio and peak postoperative total bilirubin levels within 2 weeks after surgery. A significant negative correlation was observed (P = 0.002, r = −0.295).

**Table 5** Multivariate analysis of liver dysfunction

| | *P* value | Odds ratio (95% confidence interval) |
|---|---|---|
| Hyerbilirubinemia | | |
| RLV/ELV ratio | .006 | .938 (.896–.981) |
| Blood loss | .17 | 1.000 (1.000–1.000) |
| Operative time | .09 | 1.006 (.999–1.012) |
| Fatal outcome | | |
| ICG-R15 | .041 | 1.105 (1.004–1.215) |
| RLV/ELV ratio | .005 | 0.864 (.780–.957) |
| Blood loss | .73 | 1.000 (1.000–1.000) |
| Operative time | .17 | 1.008 (0.997–1.018) |

## Logistic regression analysis

Multivariate analysis indicated that only RLV/ELV ratio was an independent risk factor that influenced hyperbilirubinemia after extended hepatic resection, as shown in Table 5. When logistic regression was used, in order to distinguish which patients had died of liver failure, ICG-R15 and, again, RLV/ELV ratio were selected as independent risk factors.

## Determination of the RLV/ELV ratio cut off value affecting postoperative hyperbilirubinemia

According to receiver operating characteristic curve, the best RLV/ELV cutoff value was 40%, with sensitivity 59% and specificity 81%, to distinguish patients with from those without postoperative hyperbilirubinemia. When RLV/ELV ratio was used in the logistic regression model as a categorical variable, instead of a continuous variable, with a cutoff of 40%, it was an independent risk factor that influenced hyperbilirubinemia after extended hepatic resection (odds ratio 7.6; 95% confidence interval, 2.1–27; $P < .002$).

## RLV/ELV ratio and ICG-R15 in patients with fatal outcome

All patients who died of liver failure had a RLV/ELV ratio of less than 40% and/or higher than 25% of ICG-R15 (Figure 3). Conversely, all patients who had RLV/ELV greater than 40% and less than 25% of ICG-R15 tolerated extended hepatic resection.

## Comments

Since extended hepatic resection was first performed to achieve curative resection, which is reported to be a major prognostic factor,[2–5,7] patient survival in cases of biliary tract malignancies has improved greatly. However, the mortality rate after extended hepatic resection is still high, ranging from 0% to 25%.[2,3,16–18] The high mortality rate is

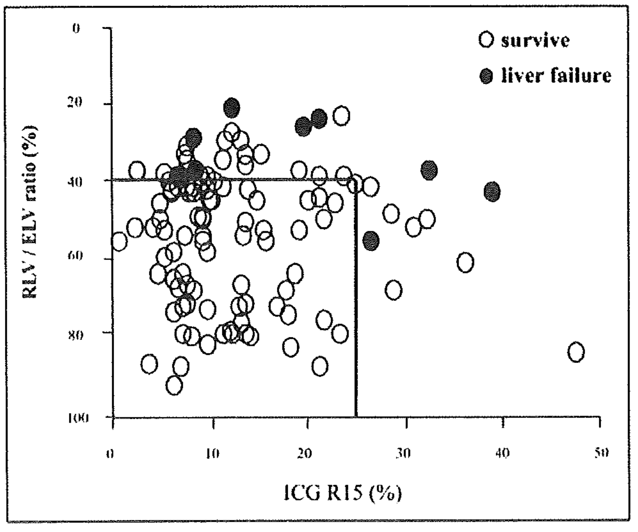


**Figure 3** RLV/ELV ratio and ICG-R15 in patients with fatal outcomes. Open circles: patients who tolerated extended hepatic resection. Filled circles: patients who died of liver failure after extended hepatic resection. All patients tolerated surgery when their RLV/ELV ratio was >40% and ICG-R15 was <25%.

mainly attributable to postoperative hyperbilirubinemia, followed by hepatic failure. Therefore, investigation of factors that influence postoperative liver dysfunction is of great interest for surgeons hoping to improve perioperative outcome in patients with biliary tract malignancies.

Since the majority of patients with biliary tract malignancies have obstructive jaundice, it has been suggested that preoperative cholestasis is associated with postoperative liver dysfunction. Many retrospective clinical reports and experimental data suggest that preoperative obstructive jaundice is related to postoperative morbidity and mortality.[19–21] Based on these facts, routine preoperative biliary decompression, to a serum bilirubin level of 2–3 mg/dL, has been advocated to reduce postoperative complications.[18,20] In the present study, all patients with obstructive jaundice received preoperative biliary drainage, but 13 (19%) of these patients still had jaundice with serum total bilirubin levels greater than 3 mg/dL at the time of extended hepatic resection. However, serum total bilirubin levels at the time of surgery and the rate of decrease in the level of serum bilirubin were not found to be significant risk factors for postoperative liver dysfunction. These results raise the question of whether or not preoperative biliary decompression should be routinely performed before extended hepatic resection, although it is possible that patients in this study who had jaundice at the time of surgery had already received effective relief of cholestasis in spite of their bilirubin levels. There have been few reports on this issue, especially in regard to patients with extended hepatic resections, but Cherqui et al[22] have recently shown that major liver resections without preoperative biliary drainage are safe for most patients with obstructive jaundice.

Our logistic regression model has shown that the RLV/ELV ratio was the strongest risk factor for liver dysfunction after extended hepatic resection in patients, the majority of whom had preoperative jaundice. Recently, with an increase of the number of cases with major hepatic resection and living-related liver transplantation, the importance of volumetric analysis by computed tomography images has been emphasized to avoid postoperative liver dysfunction.[23] Several reports have shown the minimum extent of remnant liver volume compatible with a safe postoperative outcome, with RLV/ELV ratios ranging from 25% to 30%.[8,24,25] A significant correlation between remnant liver volume and postoperative peak bilirubin level has also been reported.[8,25] These results were similar to our current results, although the extent of remnant liver volume in patients who developed postoperative hyperbilirubinemia (mean 42% of RLV/ELV ratio) and subsequent fatal outcome (mean 35% of RLV/ELV ratio) was a bit large in our study. The reason for this might be that, in previous reports, the patients who were assessed mostly had normal liver parenchyma, while in our study, the majority of patients had cholestatic liver. Takahashi et al[26] have also shown that resection of up to 48.7% of the liver was safe and hepatectomy of up to 71.6% was the maximum permissible resection, calculated on the basis of postoperative bilirubin levels, in patients with obstructive jaundice, even after relief of it. Their results and ours suggest that the extent of liver that can be safely resected is limited in the case of cholestatic liver, even after this condition is relieved, and, when the estimated RLV/ELV ratio is ≤40%, which is the critical point for postoperative liver dysfunction as shown in this study, portal vein embolization should be performed before extended hepatic resection to increase the RLV/ELV ratio.

Another significant factor for mortality due to hepatic failure, but not for postoperative hyperbilirubinemia, was ICG-R15. Use of ICG-R15 has been proposed by many institutions as one of the best ways to evaluate the safe limits for hepatic resection.[11,27] However, since such assessment is directly influenced by the severity of jaundice, due to excretory competition with bilirubin, its result must be carefully interpreted in cases of patients with obstructive jaundice. In the present study, this evaluation was conducted principally after the total bilirubin level had declined below 3 mg/dL, even in 8 of 9 patients who died after extended hepatic resection, although 13 patients who had jaundice at the time of surgery had total serum bilirubin levels greater than 3 mg/dL but not beyond 6 mg/dL at the time of ICG-R15 evaluation. Therefore, the results of ICG-R15 in patients with fatal outcomes were relatively reliable, and these results suggested that special attention should be paid to the occurrence of liver failure after extended hepatic resection in patients with high ICG-R15 even after relief of obstructive jaundice, as mentioned by Lee and Hwang[28] (wherein the livers of patients with an ICG-R15 >15% after relief of obstructive jaundice often showed diffuse parenchymal shrinkage, without evidence of liver cirrhosis). This may be an irreversible phenomenon, and hence related to cases of death due to liver failure after extended hepatic resection. In our study, no patients with ICG-R15 less than 25% died of liver failure after extended hepatic resection when their RLV/ELV ratio was greater than 40%.

In addition to preoperative volumetric parameters, intraoperative parameters may also influence postsurgical course. However, our logistic regression model failed to identify any intraoperative parameters associated with postoperative hyperbilirubinemia and also with mortality, although, in univariate analysis, the amount of blood loss during surgery and the operative time were found to be significant factors for postoperative hyperbilirubinemia. These results were similar to those in previous reports by Nagino et al[14] and Fujii et al.[29]

In conclusion, we identified RLV/ELV ratio as having the strongest impact on postoperative liver dysfunction and found that ICG-R15, evaluated after relief of jaundice, had the next strongest relationship to mortality after extended hepatic resection in patients with biliary tract malignancies. To prevent postoperative liver dysfunction, volumetric analysis should be performed in a prospective fashion; based on the results, preoperative portal vein embolization or, if possible, limited hepatic resection after precise estimation of cancer extent[30] should be considered.

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# 広範囲肝切除において術前減黄術は必須なのか？

清水宏明* 木村文夫* 吉留博之*
大塚將之* 加藤厚* 吉富秀幸*
古川勝規* 竹内男* 高屋敷吏*
須田浩介* 宮崎勝*

索引用語：胆道癌，閉塞性黄疸，胆道ドレナージ，肝切除

## 1 はじめに

胆道癌診療ガイドライン[1]では，「胆管炎，広範囲肝切除予定例に術前減黄術が必要である．」というクリニカルクエスチョンに対して推奨度B，つまり，胆管ドレナージを行うよう勧めるという回答を示している．ガイドラインでは，胆管炎に関しての解説はなされてないものの，これまでに多くの論文で胆管炎は肝切除術後の肝不全発生のリスクファクターの一つであるとが報告されており[2]，欧米でも閉塞性胆管炎に対しての胆道ドレナージの施行は異論のないところであろう．その一方，胆管炎の合併を認めない閉塞性黄疸患者に対する術前胆管ドレナージの臨床的意義はいまだ明らかでないのが現状である．欧米においてはむしろ胆道ドレナージ，とくにPTBDの合併症による弊害がみられたとする報告さえもある[3-5]．さらに，最近の画像診断の進歩に伴い，とくにMultidetector-row CT（MDCT）の登場以来，Multiplanar reconstruction（MPR）をはじめとする再構成法（図1），さらには，MR cholangiographyの精度も飛躍的な進歩[6]をとげており，以前ほど直接胆管造影での長軸方向への癌の進展度診断の必要性がなくなってきたことも事実である．本邦でも，術前減黄に対する考え方も少しずつ変化してきており，肝切除を要さない中下部胆管閉塞では，術前胆道ドレナージは必須ではない[7]（肝機能不良例などを除けば）とのコンセンサスも得られつつある．しかしながらこれもRCTによるエビデンスレベルの高いstudyによって裏付けられているわけではない．その一方で，術後肝不全を中心とした合併症率の高い黄疸を伴う患者に対しての広範囲肝切除例では，本邦ではほぼ全例，

*Hiroaki SHIMIZU et al* : Significance of preoperative biliary drainage in patients with obstructive jaundice before extended hepatectomy
*千葉大学大学院医学研究院・臓器制御外科学［〒260-8677 千葉市中央区亥鼻1-8-1］

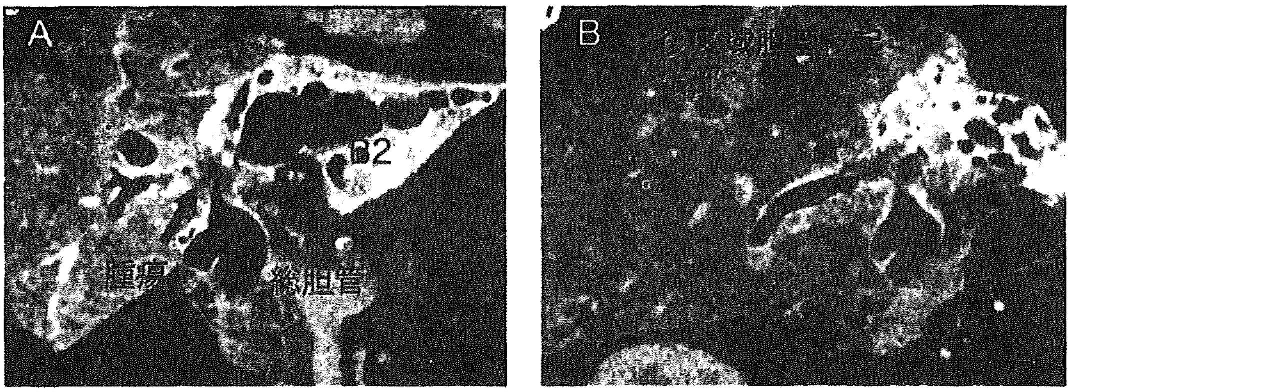


図1 肝門部胆管癌症例のMD-CT（MPR冠状断像）
肝実質に比し軽度低吸収域として肝門部に描出される腫瘍を認める.
（B）後区域胆管枝起始部まで腫瘍の浸潤を認める.

術前減黄術が行われているのが現状である[8〜10]. これは, 以下に示す基礎的研究, 後ろ向きの研究の結果をよりどころとして施行されており, その科学的意義を明らかにするための多数例を対象としたRCTの結果に基づいている訳ではない. したがって, 全国レベルでのRCTが今後, 期待されるところであるが, 実際には術後死亡率の高い疾患を対象としてのRCTの実現は極めて困難であろう.

この項では最近報告された論文, さらには基礎的研究より, 黄疸症例における術前減黄術の意義についてのエビデンスをまとめ, 広範囲肝切除が予定された際の術前減黄術の適応についての再考してみた.

## 2 基礎実験からみた肝切除前の減黄術の有用性について

閉塞性黄疸肝では正常肝と比較し, 細胞障害に結びつくさまざまな変化が生じていることが基礎的研究により示されてきた. すなわち, 黄疸期間の延長とともに肝組織血流量は低下し, 肝細胞膜障害も惹起される[11]. さらに肝ミトコンドリア機能の障害も認められ[12], 血漿中・肝組織中に高値となる胆汁酸はこのミトコンドリア機能障害を介して[13], あるいはFasを介して肝細胞のアポトーシスを誘導する[14]と報告されている. また, 免疫能からみてみると腸管内胆汁の欠如により, 腸管内のCD8陽性Tリンパ球とマクロファージ数は減少し[15], さらにKupffer細胞のサイトカイン産生性もTh2優位の状態となり[16], 門脈血中・肝へのbacterial translocationが容易に発生しやすい状況となっている. また, その一方で, 胆道ドレナージ（とくに内瘻化）を図ることによって, これらの閉塞性黄疸時に障害された機能がある程度改善し得ることも報告されている[17]. さらに, 閉塞性黄疸時には, 抱合型ビリルビンの胆汁への排泄に必要不可欠な輸送蛋白であるmultidrug resistance protein 2（MPR2）の肝細胞毛細胆管膜での発現が低下し, 肝切除術後の高ビリルビン血症が発生しやすい病態であるとされる[18]. われわれもラット70%肝切除モデルを用いて, 閉塞性黄疸が肝切除後の肝再生に及ぼす影響を残肝組織中の増殖因子/抑制因子の発現の推移より検討してみたところ, 閉塞性黄疸によりIto細胞の数の増

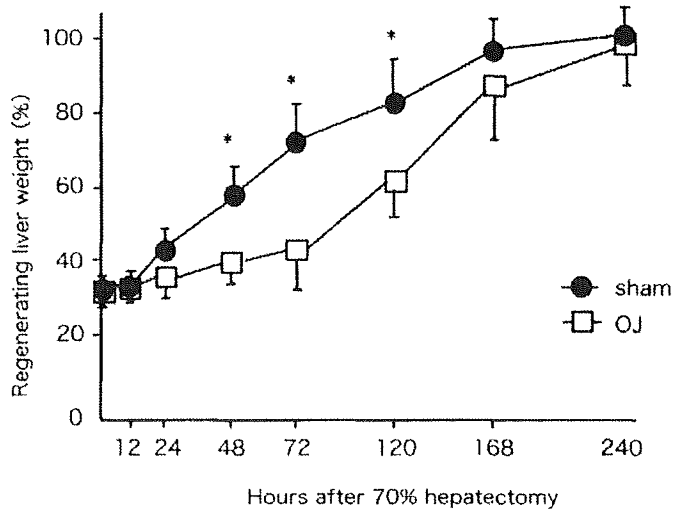


図2　閉塞性黄疸(OJ)群(ラット胆管結紮2週間)とsham群における70%肝切除施行後に再生肝重量の変化
OJ群の肝再生はsham群に比し，有意に遅延(*p<0.05).

加と活性化が起こり，肝切除後にはその活性化したIto細胞からのTGF-β1産生亢進とHGFの産生低下により，有意に肝再生は抑制・遅延する(図2)結果を得ている[19].

このように閉塞性黄疸時の肝切除後には容易に肝障害，高ビリルビン血症，肝再生抑制さらには感染性合併症が引き起こされやすい状態となっているわけである．したがって，胆道ドレナージによってある程度その病態の改善が期待し得ることから，実際の臨床，とくに術後肝不全による死亡率の高い，胆道癌の広汎肝切除が予定される症例においては，術前減黄術を実施する意義があるだろうと考えられるわけである．

## 3 肝切除前の減黄術についての臨床的検討について

本邦でもMR cholangiography，MDCTなどの各種画像診断から，外科切除に際し，肝切除を要さない中下部胆管閉塞(中下部胆管癌，乳頭部癌，膵癌)は，術前胆管ドレナージによる減黄は必要としないとする報告[7]も多数みられており，この点では術前減黄に関しての考え方も変わりつつある．しかしながら，その一方で，手術関連死亡率が高いとされる広範肝切除術を選択することが多い肝門部胆管癌[8～10,20,21]，肝門浸潤を伴う胆嚢癌[22]ではその肝機能の面から，さらには挿入されたドレナージチューブからの胆管造影による進展度診断法としての意味合いから，術前に胆管ドレナージを挿入し，十分に減黄を待って根治手術を行うのが，本邦では一般的なstrategyとされる．

現在まで閉塞性黄疸を伴った症例での拡大肝切除術における検討はCherquiら[23]による報告(n = 20)が唯一あるのみである．この論文では術前胆道ドレナージなしで施行した拡大肝葉切除の成績は，手術関連死亡率5%，術後合併症率50%であり，閉塞性黄疸を伴わない症例とほぼ同様な手術関連死亡率であったとしている．これは本邦からの報告，すなわち術前胆道ドレナージを施行し，十分