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Surgical Anatomy of the Bile Ducts at the Hepatic Hilum as Applied to Living Donor Liver Transplantation

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Objective: To evaluate anatomic variations of the biliary tree as applied to living donor liver transplantation.

Summary Background Data: Anatomic variability is the rule rather than the exception in liver surgery. However, few studies have focused on the anatomic variations of the biliary tree in living donor liver transplantation in relation to biliary reconstruction.

Methods: From November 1992 to June 2002, 165 patients underwent major hepatectomy with extrahepatic bile duct resection; right-sided hepatectomy in 110 patients and left-sided hepatectomy in 55. Confluence patterns of the intrahepatic bile ducts at the hepatic hilum in the surgical specimens were studied.

Results: Confluence patterns of the right intrahepatic bile ducts were classified into 7 types. The right hepatic duct was absent in 4 of the 7 types and in 29 (26%) of the 110 livers. Confluence patterns of the left intrahepatic bile ducts were classified into 4 types. The left hepatic duct was absent in 1 of the 4 types and in 1 (2%) of the 55 livers.

Conclusions: In harvesting the right liver from a donor without a right hepatic duct, 2 or more bile duct stumps will be present in the plane of transection in the graft in 3 patterns based on their relation to the portal vein. Accurate knowledge of the variations in the hepatic confluence is essential for successful living donor liver transplantation.

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Living donor liver transplantation (LDLT) is an accepted alternative for patients waiting for cadaveric liver transplantation, especially in countries where the availability of brain-dead donors is severely restricted. The evolution of this procedure has expanded its applicability to the right liver lobe donations.[1,2] A precise understanding of general anatomic principles and common variations is the key to safe LDLT. Despite extensive work on the anatomic and technical aspects of LDLT,[3] few studies have focused on the anatomic variations of the biliary tree in relation to the safety of bile duct division and reconstruction.[4] Misunderstanding of the biliary anatomy can lead to severe postoperative complications.[5] Therefore, we studied the anatomic variations of the biliary tree based on our clinical experience with biliary malignancies to enhance the safety of LDLT.

PATIENTS AND METHODS

Between November 1992 and June 2002, 165 patients underwent major hepatectomy with extrahepatic bile duct resection: right-sided hepatectomy (right hepatectomy and right trisectionectomy) in 110 patients and left-sided hepatectomy (left hepatectomy and left trisectionectomy) in 55. Surgical specimens were used for this study.

After performing cholangiography on the specimen, the extrahepatic bile duct was opened longitudinally from the distal margin of resection to the proximal margin. The specimen was fixed in 10% formalin for several days and serially sectioned at 5-mm intervals. Intrahepatic segmental and subsegmental ducts and extrahepatic bile ducts were identified on the serial sections according to our classification system, which is similar to Couinaud's classification.[6–8] Subsegmental areas of the liver were identified initially, followed by identification of biliary ducts from the subsegmental ducts to the segmental and sectional ducts. The bile ducts in each section was reconstructed three-dimensionally and drawn on a paper two-dimensionally. We refer to this technique as the "pressed flower method." Histologic extension of cancer along the bile ducts was mapped in each scheme (Fig. 1). Confluence patterns of the bile ducts at the hepatic hilum were determined using these two-dimensional records. Surgical specimens of right-sided hepatectomies (n = 110) were used to study the confluence patterns of the right intrahepatic and extrahepatic bile ducts (the right anterior and posterior sectional bile ducts, and the right and common hepatic ducts). Surgical specimens of left-sided hepatectomies (n = 55) were used to study confluence patterns of left intrahepatic and

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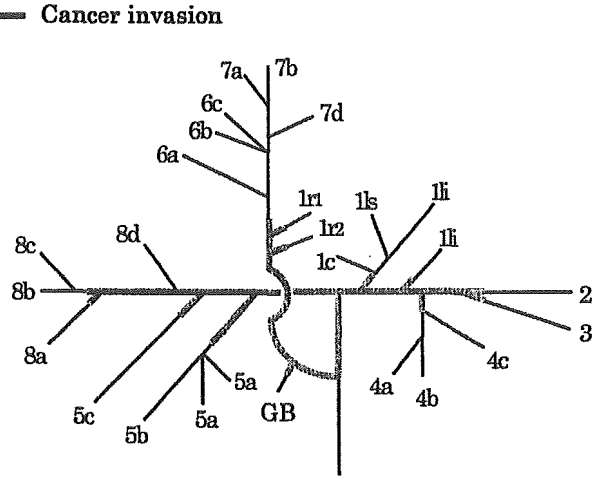

FIGURE 1. Two-dimensional map of the confluence patterns of intrahepatic and extrahepatic bile ducts and cancer extension along the bile ducts (the "pressed flower method"). Numbers refer to the Couinaud's segment. 1li, left inferior branch; 1ls, left superior branch; 1c, caudate process branch; 1r, right branch; 4a, inferior branch; 4b, superior branch; 4c, dorsal branch; 5a, ventral branch; 5b, dorsal branch; 5c, lateral branch; 6a, ventral branch; 6b, dorsal branch; 6c, lateral branch; 7a, ventral branch; 7b, dorsal branch; 7d, medial branch; 8a, ventral branch; 8b, lateral branch; 8c, dorsal branch; 8d, medial branch; and GB, gallbladder.

extrahepatic bile ducts (the left lateral anterior and posterior segmental ducts, the left medial segmental bile duct, and the left and common hepatic ducts).[9]

RESULTS

Confluence Patterns of the Right Intrahepatic Bile Ducts

Confluence patterns of the right intrahepatic bile ducts were classified into three patterns according to the anatomic relation between the right posterior sectional bile duct and the portal vein (Fig. 2): supraportal pattern (n = 91) in which the right posterior sectional bile duct ran dorsally and cranially to the right or the right anterior portal vein and joined with the distal bile duct at its cranial side; infraportal pattern (n = 13) in which the right posterior sectional bile duct ran ventrally and caudally to the right or the right anterior portal vein and drained into the distal bile duct at its caudal side; and combined pattern (n = 6) in which some parts of the right posterior sectional bile duct entered the distal bile duct supraportally and the remaining parts of the right posterior sectional bile duct joined with the distal bile duct infraportally. The 91 cases of the supraportal pattern were classified into three subtypes (Fig. 3): the right posterior sectional bile duct joined with the right anterior sectional bile duct, forming the right hepatic duct (type A, n = 72); the right posterior sectional bile duct entered the confluence of the right anterior sectional bile duct and the left hepatic duct (type B, n = 6); the right posterior sectional bile duct drained into the left hepatic duct (type C, n = 13). In 1 of the 72 type A cases, a dorsal subsegmental branch of the right anterior inferior bile duct joined with the cystic duct. The 13 cases with the infraportal pattern were classified into two subtypes: the right posterior sectional bile duct joined with the right anterior sectional bile duct, forming the right hepatic duct (type D, n = 8); and the right posterior sectional bile duct entered the common hepatic duct (type E, n = 5). Six cases of a combined pattern also were classified into two subtypes: a portion of the right posterior sectional bile duct joined with the right anterior sectional bile duct infraportally, becoming the right hepatic duct, and the remaining parts of the right posterior sectional bile duct entered the right hepatic duct supraportally (type F, n = 1); and a portion of the right posterior sectional bile duct joined with the common hepatic duct infraportally and the remaining parts entered the left hepatic duct supraportally (type G, n = 5). The right hepatic duct was absent in types B, C, E, and G.

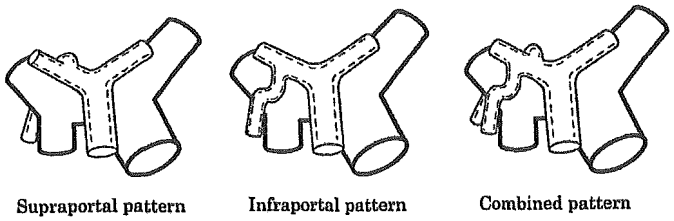

FIGURE 2. The three confluence patterns of the right posterior sectional bile ducts according to their anatomic relationship to the right portal vein.

Confluence Patterns of the Left Intrahepatic Bile Ducts

Confluence patterns of the left intrahepatic bile ducts were classified into four types according to confluence patterns of the left medial sectional bile duct (Fig. 4). The left medial sectional bile duct drained into the left lateral sectional bile duct in type H (n = 43); the left medial sectional bile duct entered the confluence of the left lateral anterior and posterior segmental bile ducts in type I (n = 2); the left medial sectional bile duct joined with the left lateral anterior segmental bile duct in type J (n = 9); the left medial sectional bile duct entered the hepatic confluence in type K (n = 1); and the left hepatic duct was absent in type K. In one case of type J, the left lateral anterior segmental bile duct ran caudally to the umbilical portion of the left portal vein: (type J').

DISCUSSION

Compared with cadaveric liver transplantation, LDLT offers several advantages: a large number of organs available for children; elective basis for transplantation, resulting in

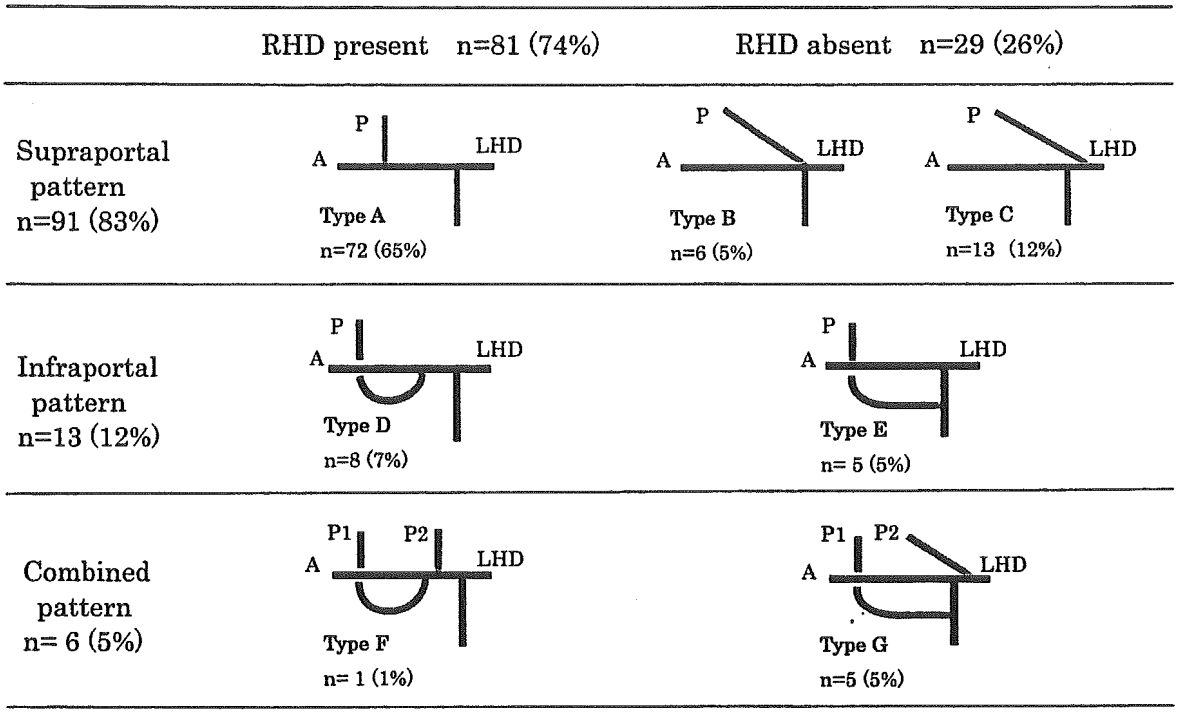

FIGURE 3. Confluence patterns of the right intrahepatic bile ducts in 110 cases. Supraportal pattern: Type A, the right posterior sectional bile duct (P) joins the right anterior sectional bile duct (A); Type B, P drains into the confluence of A and left hepatic duct (LHD); and Type C, P enters LHD. Infraportal pattern: Type D, P joins A; Type E, P enters the common hepatic duct. Combined pattern: Type F, some elements of the right posterior sectional bile duct (P1) enter A infraportally and the remaining portion (P2) joins A supraportally; and Type G, P joins the common hepatic duct infraportally and P2 joins LHD supraportally. RHD, right hepatic duct.

lower morbidity, mortality, and overall cost; the absence of primary nonfunction resulting from minimal cold ischemia time and the use of healthy donor; and theoretical immunologic advantages, as suggested by a lower incidence of steroid-resistant rejection.[10] Despite these technical and immunologic advantages, biliary complications remain one of the most common problems in LDLT and occur in approximately 30% of the cases.[10,11] Careful attention to the bile duct must be paid not only in recipients but also in the donor organ. As anatomic variations of the biliary tree are very common, incomplete appreciation of the segmental biliary anatomy can lead to complications. Although Huang et al[12] studied the confluence patterns of the biliary tree using endoscopic retrograde cholangiography, this is the first study to report anatomic variations of the hepatic confluence in relationship to the portal vein using surgical specimens.

As right liver harvesting has become increasingly common,[13,14] knowledge of the anatomic variations of the right intrahepatic bile ducts is very important. In the current study, the right hepatic duct was absent in 29 (26%) of the 110 cases. When harvesting a donor without a right hepatic duct, two or more orifices of the bile ducts will be present in plane of transection of the graft. Biliary reconstruction of these

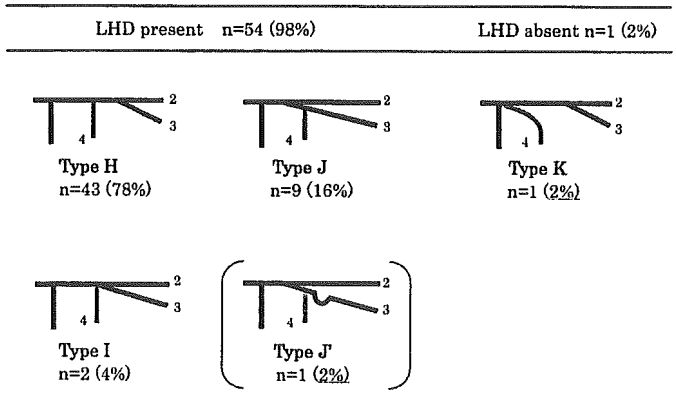

FIGURE 4. Confluence patterns of the left intrahepatic bile ducts in 55 cases. Type H, the left medial sectional bile duct[4] enters the left lateral sectional bile duct. Type I, 4 enters the confluence of the left lateral anterior[3] and posterior[2] segmental bile ducts; Type J, 4 enters 3; Type J', 3 runs caudally to the umbilical portion of the left portal vein; and Type K, 4 enters the hepatic confluence. LHD, left hepatic duct.

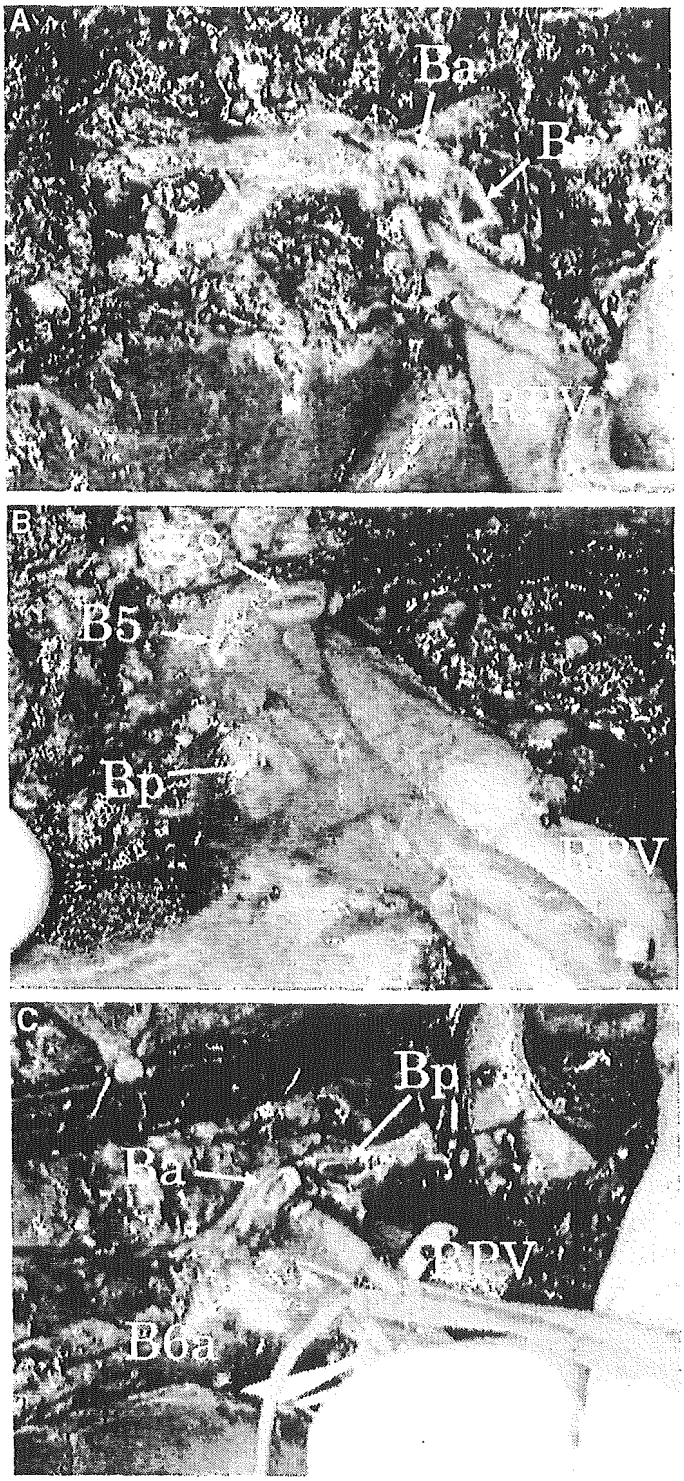

FIGURE 5. Intraoperative photographs of the plane of transection of the liver after left hepatectomy with caudate lobectomy, which is similar to the transection plane of the right liver graft. A: Supraportal pattern. The orifice of the right posterior sectional bile duct (Bp) is opened cranial to the right anterior portal vein. B: Infraportal pattern. Bp is opened caudal to the right anterior portal vein. C: Combined pattern. Stumps are present cranially and caudally to the right anterior portal vein. RPV, right portal vein; Ba, right anterior sectional bile duct; B5, right anterior inferior segmental bile duct; B8, right anterior superior segmental bile duct; and B6a, ventral subsegmental branch of the right posterior inferior segmental bile duct.

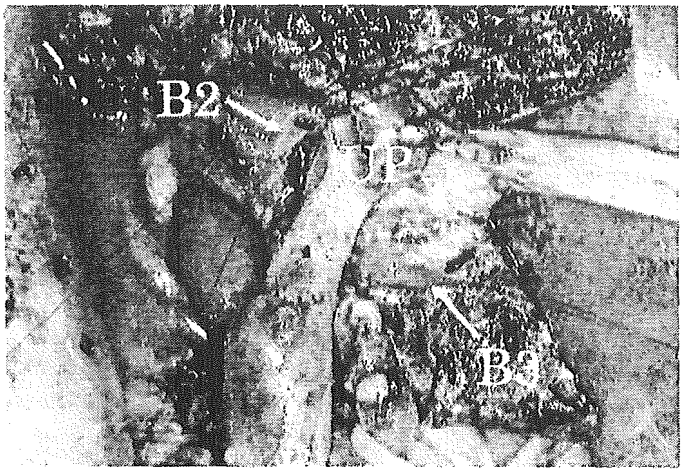

FIGURE 6. Intraoperative photograph of the plane of transection of the liver after right trisectionectomy and caudate lobectomy combined with portal vein resection and reconstruction in a patient with type J' anatomy. The bile duct stumps can be seen on both sides of the umbilical portion of the left portal vein (UP). B2, left lateral posterior segmental bile duct; and B3, left lateral anterior segmental bile duct.

variants is complicated and technically difficult. When the supraportal pattern is present (types B, C), the stump of the right posterior sectional bile duct is present cranial to the right anterior portal vein (Fig. 5A). In cases of the infraportal pattern (type E), the orifice opens caudally to the right anterior portal vein (Fig. 5B). In cases of the combined pattern (type G), stumps are present both cranially and caudally (Fig. 5C). It is essential that both stumps must be reconstructed when they are present. Furthermore, particular care must be taken in harvesting the left liver from a donor with a type C or G variant. As the right posterior sectional bile duct will be divided from the left hepatic duct in these cases, oversight or ligation of the stump of the right posterior sectional bile duct will lead to biliary leakage or obstruction in the donor.

Although the confluence pattern of the left intrahepatic bile ducts has been reviewed by Reichert et al,[15] they did not encounter the type K variant. When harvesting the left liver from a donor with this rare variant, overlooking the stump of the left medial sectional bile duct will lead to biliary complications. Type J' also is a rare, but critical, variant. In harvesting the left lateral section from a donor with this variant, stumps of the left lateral posterior and anterior segmental bile

ducts are open cranial and caudal to the umbilical portion of the left portal vein, respectively (Fig. 6). The stump of the left lateral anterior segmental bile duct can easily escape the notice.

In LDLT, the biliary anatomy of the donor usually is evaluated using intraoperative cholangiography.[1,16] The surgeon must make a snap decision as to the biliary anatomy and its relationship to the line of transection. When the right posterior sectional bile duct drains into the left hepatic duct, it runs supraportally; and when the right posterior sectional bile duct enters the common hepatic duct, it runs infraportally. Familiarity with the variations of the hepatic confluence, especially types B, C, E, G, J', and K, will decrease the likelihood of surgical misadventure.

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Changes in Splenic Volume during Liver Regeneration

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Abstract. Little is known about the relation between liver regeneration and splenic size. We monitored serial changes in liver and spleen volumes using computed tomography in 24 patients with biliary cancer who underwent right hepatectomy or more extensive liver resection following portal vein embolization (PVE). Nonembolized hepatic segments increased in volume from 316 ± 97 cm^3 (34% ± 8% of total liver volume) before PVE to 410 ± 115 cm^3 (44% ± 8%) after PVE. The volume of nonembolized hepatic segments (i.e., remnant liver) increased to 617 ± 111 cm^3 (59% ± 10% of total liver volume before PVE) 14 days after hepatectomy and then increased slowly to reach 795 ± 231 cm^3 (76% ± 16%) 1 year after hepatectomy. Splenic volume increased from 87 ± 29 cm^3 before PVE to 104 ± 38 cm^3 (119% ± 17% of original volume) after PVE. Splenic volume increased to 137 ± 65 cm^3 (155% ± 40%) by 14 days after hepatectomy and to 155 ± 67 cm^3 (179% ± 41%) by 28 days after hepatectomy, with no further change at 1 year after hepatectomy (153 ± 92 cm^3; 174% ± 79%). The rate of increase in splenic volume within the first 14 days after hepatectomy was 2.7 ± 3.6 cm^3/day, correlating well with increases in remnant liver volume ($r = 0.64$, $p = 0.0006$). These data indicate that the spleen is enlarged during liver regeneration, suggesting that the liver and spleen share certain common growth regulatory mechanisms.

Since ancient times, the liver has been known to regenerate after loss of hepatic mass. Many authors have determined liver volume after hepatectomy using computed tomography (CT), confirming that the human liver has good regenerative capacity and that regeneration is influenced by the resection volume and the presence of coexisting liver disease [1–6]. Experimental evidence suggests that splenic factors suppress liver regeneration after hepatectomy [7–9], but only one clinical study [10] has considered splenic size as a possible factor in this suppression. Because no studies have included measurements of splenic volume during liver regeneration, little is known about the relation between liver regeneration and splenic volume.

Recently, portal vein embolization (PVE) has been widely adopted as a treatment before performing extensive liver resection [11, 12]. Both experimental and clinical studies demonstrated that PVE induces regeneration in nonembolized hepatic segments [13–16]. In the present study, we measured changes in splenic volume by CT after two regenerative stimuli, PVE and then hepatectomy, to elucidate the relation between splenic volume and liver regeneration.

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Materials and Methods

From January 1999 to January 2002 a total of 32 patients with biliary cancer underwent right hepatectomy or more extensive liver resection after PVE at the First Department of Surgery, Nagoya University Hospital. Among them, 24 patients were involved in this study, because they underwent CT before and after PVE and at 14 days, 28 days, and 1 year after hepatectomy. Times between PVE and the subsequent CT after PVE were 16.2 ± 4.9 days (median 14 days; range 8–25 days). Hepatectomy was carried out 1 or 2 days after the post-PVE CT.

The subjects included 10 men and 14 women, with an average age of 66.0 ± 7.3 years. Altogether, 18 patients had proximal cholangiocarcinoma, and the remaining 6 had advanced gallbladder carcinoma involving the hepatic hilus. Tumor staging was evaluated using the TNM Classification of Malignant Tumors by the International Union Against Cancer [17] (Table 1). No patient was cirrhotic. All patients had obstructive jaundice on admission, but none had jaundice at the time of PVE, as they had undergone percutaneous transhepatic biliary drainage. All patients underwent curative resection and showed no recurrence for at least 1 year.

Surgical procedures performed are summarized in Table 1. En bloc resection of the extrahepatic bile duct was performed in all patients, and bilioenteric continuity was reestablished by hepaticojejunostomy using a Roux-en-Y jejunal limb. Embolized portal vein(s) were the right portal vein and left medial portal branch preceding right hepatic trisectionectomy [18] (resection of Couinaud's segments 4, 5, 6, 7, and 8), the left portal vein and the right anterior portal branch preceding left hepatic trisectionectomy (resection of segments 2, 3, 4, 5, and 8), or the right portal vein preceding right hepatectomy (resection of segments 5, 6, 7, and 8) [19, 20] Accordingly, except for the caudate lobe, embolized hepatic segments corresponded precisely to the resected segments in this series.

Volumetric measurements of the liver and spleen were performed by methods previously reported [2, 6, 15]. Briefly, serial transverse images of the upper abdomen were obtained at 1 cm intervals, with enhancement by intravenous bolus injection of contrast medium. Each slice of the liver and spleen was traced with the

Table 1. Surgical procedures performed in 24 patients.

Parameter	No. of patients
TNM staging[a]	
T2	4
T3	5
T4	15
N0	14
N1	10
M0	23
M1	1
Tumor stage	
IB	4
IIA	3
IIB	3
III	13
IV	1
Type of hepatectomy[b]	
S1, 4, 5, 6, 7, 8	4
S1, 4a,[c] 5, 6, 7, 8	4
S1, 5, 6, 7, 8	13
S1, 2, 3, 4, 5, 8	3

[a]According to *TNM Classification of Malignant Tumors* by the UICC (6th edition).
[b]Expressed as Couinaud's hepatic segments (S1 through S8) resected.
[c]4a: Segment 4.

cursor, and the corresponding area was calculated by computer. Total volumes of the liver and spleen were obtained by adding the volumes of individual slices. All volumetric measurements were carried out by a single doctor (H.A.) to eliminate interobserver variability. An indocyanine green (ICG) test was carried out within 1 week before surgery according to a method described elsewhere [21]; it was expressed as plasma clearance rate of indocyanine green (KICG). Body surface area (BSA) was calculated using the equation of DuBois and DuBois [22].

$$BSA\ (m^2) = \text{body weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184$$

Results are expressed as the mean ± SD. Statistical analysis was performed with the paired Student's *t*-test. All *r* values were defined using Pearson's correlation coefficient. A level of $p < 0.05$ was considered statistically significant.

Results

Serial Changes in Volumes of Nonembolized Hepatic Segments and Spleen

Total liver and splenic volumes before PVE were 1048 ± 160 cm^3 (range 726–1318 cm^3) and 87 ± 29 cm^3 (range 27–146 cm^3), respectively. The liver volume before PVE correlated well with the BSA ($r = 0.68, p < 0.0001$). The splenic volume before PVE showed a significant negative correlation with age ($r = -0.41, p < 0.05$) but not with the BSA ($r = 0.14, p = 0.523$) or KICG ($r = -0.08, p = 0.720$).

The volume of nonembolized hepatic segments (excluding the caudate lobe) increased from 316 ± 97 cm^3 (34% ± 8% of total liver volume) before PVE to 410 ± 115 cm^3 (44% ± 8%) after PVE. However, total liver volume after PVE was unchanged (1039 ± 170 cm^3) as the volume of embolized hepatic segments decreased. The volume of nonembolized hepatic segments (i.e., remnant liver) increased to 617 ± 111 cm^3 (59% ± 10% of total liver volume before PVE) 14 days after hepatectomy and then slowly increased to reach 795 ± 231 cm^3 (76% ± 16%) 1 year after hepatectomy (Fig. 1). The liver volume 1 year after hepatectomy correlated strongly with the BSA ($r = 0.85, p < 0.0001$).

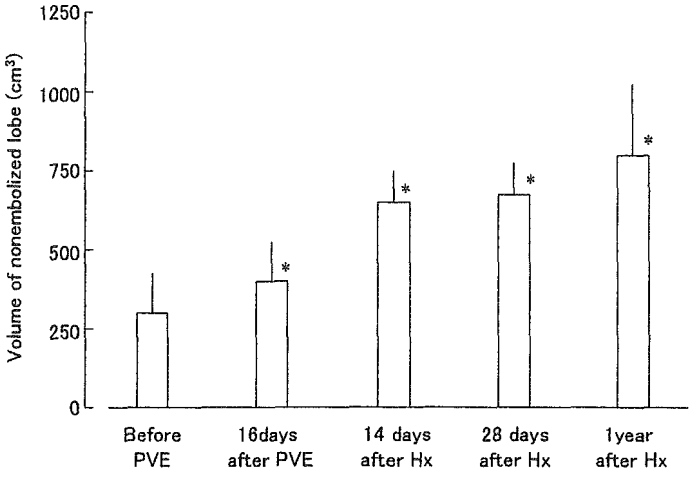

Fig. 1. Changes in nonembolized (remnant) liver volume. PVE: portal vein embolization; Hx: hepatectomy. *$p < 0.001$ versus before PVE.

The splenic volume increased from 87 ± 29 cm^3 before PVE to 104 ± 38 cm^3 (119% ± 17% of original volume) after PVE. The volume increased to 137 ± 65 cm^3 (155% ± 40%) by 14 days after hepatectomy and to 155 ± 67 cm^3 (179% ± 41%) by 28 days after hepatectomy. The volume had not changed further 1 year after hepatectomy (153 ± 92 cm^3; 174% ± 79%) (Fig. 2). The splenic volume 1 year after hepatectomy exhibited no correlations with BSA ($r = 0.27, p = 0.204$), KICG ($r = -0.04, p = 0.847$), or liver volume 1 year after hepatectomy ($r = 0.29, p = 0.167$).

Association between Liver Regeneration and Splenic Volume

The rate of increase in the volume of nonembolized hepatic segments after PVE was 6.2 ± 3.1 cm^3/day, and that of the spleen was 1.0 ± 1.0 cm^3/day. No correlation was found between these two rates ($r = 0.12, p = 0.579$).

The rate of increase in the remnant liver volume within 14 days after hepatectomy was 16.3 ± 9.3 cm^3/day, and that of the spleen was 2.7 ± 3.6 cm^3/day. A significant correlation was found between these two rates ($r = 0.64, p = 0.0006$) (Fig. 3). The rate of increase in the remnant liver volume within 14 days after hepatectomy correlated with neither the splenic volume before PVE ($r = 0.28, p = 0.189$) nor that after PVE ($r = 0.28, p = 0.183$).

Association between Splenic Volume and Platelet Count

The platelet count was unchanged before and after PVE. However, it decreased to 19.8 ± 6.5 × $10^4/\mu l$ 28 days after hepatectomy and then slowly decreased to reach 15.9 ± 4.7 × $10^4/\mu l$ (62.3% ± 20.8% of the value before PVE) 1 year after hepatectomy (Fig. 4). Before PVE there was no correlation between the splenic volume and the platelet count, whereas 1 year after hepatectomy a significant negative correlation was found between these two parameters ($r = -0.411, p = 0.0456$).

Discussion

Many authors have investigated liver size in adult populations, finding that the liver volume in adults correlates well with the BSA [6,

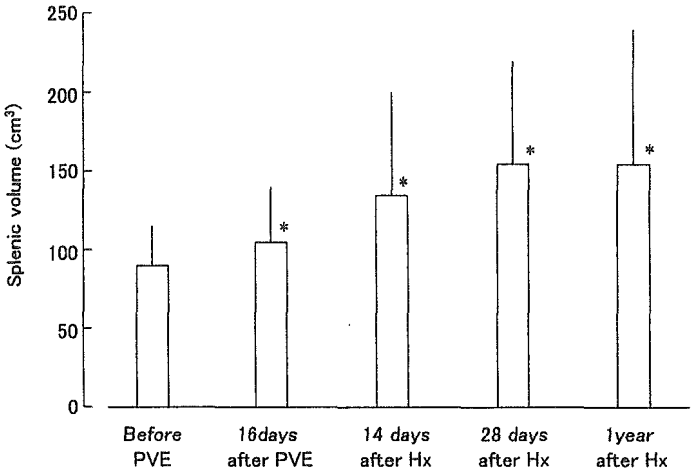

Fig. 2. Changes in splenic volume. *$p < 0.001$ versus before PVE.

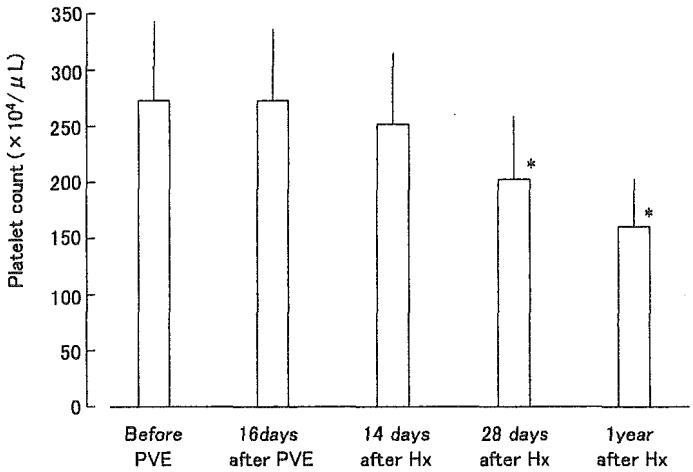

Fig. 4. Changes in platelet count. *$p < 0.001$ versus before PVE.

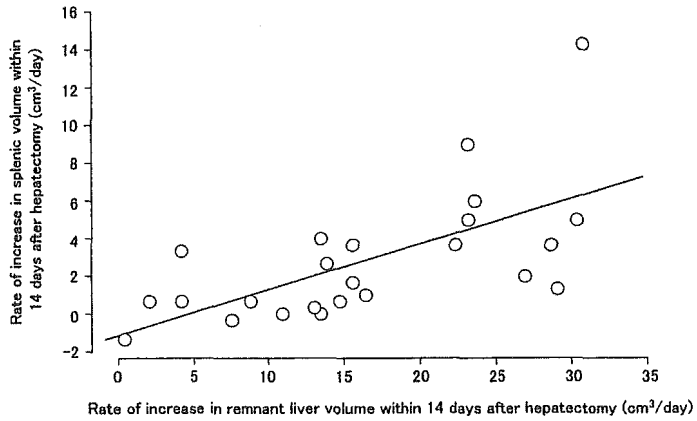

Fig. 3. Correlation between rate of increase in volume of remnant liver within 14 days after hepatectomy and rate of splenic volume increase ($r = 0.64, p = 0.0006$).

23]. In contrast, no criteria for normal splenic volume have been widely accepted. Using CT, Henderson et al. [24] reported the first measurement of splenic volume in vivo. In 11 normal Caucasians 20 to 30 years old, it was 219 cm^3. Prassopoulos et al. [25] also measured splenic volume in 140 Caucasians, finding that the mean splenic volume was 215 cm^3 and that splenic volume had no correlation with age or BSA. More recently, Kaneko et al. [26] studied splenic volume in 150 healthy Japanese donors for liver transplantation (mean age 36 years, range 20–63 years), finding the mean value to be 112 ± 40 cm^3 (range 39–209 cm^3). They also found that splenic volume correlated negatively with age but not with the BSA. In our present study, the pretreatment splenic volume was 87 ± 29 cm^3. Considering the difference in the mean age of the subjects, our data are compatible with those of Kaneko et al. Importantly, the splenic volume showed no correlation with BSA, unlike the liver volume. Although a negative correlation between age and splenic volume was found, the correlation coefficient was small (0.36 in the Kaneko et al. series and 0.41 in ours), making the relation less clinically important. Considering all data, the main determinant of adult splenic volume is still unclear.

We demonstrated an increase in splenic volume during liver regeneration to 119% ± 17% of the original volume by 16 days after PVE and to 155% ± 40% by 14 days after hepatectomy. The rate of increase in splenic volume was 1.0 cm^3/day after PVE and 2.7 cm^3/day after hepatectomy, whereas the rate of increase in the volume of the nonembolized (i.e., remnant) hepatic segments was 6.2 cm^3/day after PVE and 16.3 cm^3/day after hepatectomy. Interestingly, the ratio of the volume increase rate after hepatectomy to that after PVE were similar for the spleen (2.7/1.0 = 2.7) and the liver (16.3/6.2 = 2.6). In addition, a significant correlation was found between the rate of increase in the remnant liver volume after hepatectomy and that of the splenic volume after hepatectomy. Portal venous pressure increases after major hepatectomy [27–29], but the increase is reported to be small, less than 4 or 5 cm H_2O, and the portal venous pressure returns to near the prehepatectomy level within 7 days. Therefore passive congestion due to increased portal venous pressure may be of only limited importance as a determinant and mechanism of the splenic volume increase. Instead, our results suggest that the liver and spleen may share certain growth regulatory mechanisms.

The spleen has been shown to be capable of regeneration after partial splenectomy or autotransplantation of splenic fragments following splenectomy [30–32], although the regenerative process in the spleen is not as striking as that in the liver. In addition, a study of carbon tetrachloride-induced liver injury demonstrated not only liver regeneration but also increased growth of such splenic autotransplants [31]. Charters et al. [32] showed that uptake of [^{3}H]thymidine in rat spleen after a 70% hepatectomy tripled and peaked at 24 hours, a time course similar to that of maximal uptake for hepatocytes. This observation of an early peak of DNA synthetic activity in the liver and spleen following hepatectomy supports the hypothesis that both cell populations may be responding to common stimulating factors, possibly including hepatocyte growth factor, epidermal growth factor, transforming growth factor-a, or a combination of these factors [33–37]. Our results also support this hypothesis.

One year after hepatectomy, the remnant liver volume increased to 76% of the original volume, and the spleen volume remained increased to 174% of the original volume. Yanaga et al. [38] reported that the increased splenic volume in patients with cirrhosis and hypersplenism was reduced after orthotopic liver transplantation performed as radical therapy for portal hypertension. Even if the portal pressure increases immediately after hepatectomy, it re-

turns to preoperative values at an early stage after hepatectomy [28, 29]. Therefore we suspect that the increased volume of the spleen observed in the present study is not a result of passive congestion. Rather, it represents regeneration of the spleen. Previously, we demonstrated that liver regeneration stops when the liver attains three-fourths of its original volume approximately 6 months to 1 year after hepatectomy [6]. In other words, the remnant liver after hepatectomy does not return to its original volume. The liver and spleen are important components of the reticuloendothelial system and have approximately equal numbers of reticuloendothelial cells [32]. Increases in the volume of the spleen after hepatectomy may be a mechanism to maintain the available reticuloendothelial cell mass. Unlike the liver, however, the splenic volume 1 year after hepatectomy had no correlation with the BSA, KICG, or liver volume. Therefore the determinant of splenic volume after hepatectomy remains unknown.

The platelet count decreased to nearly 60% of the original value 1 year after hepatectomy, possibly resulting from increased splenic volume, because a significant negative correlation was found between the splenic volume and the platelet count 1 year after hepatectomy. Akimaru et al. [39] reported that a reducted platelet count occurs only in patients with cirrhosis or chronic hepatitis who underwent major hepatectomy. In their series, however, the follow-up was extraordinarily short, limited to the hospital stay. An important fact is that even in noncirrhotic patients the platelet count decreases significantly after major hepatectomy.

In several experimental studies [7–9], splenectomy accelerated liver regeneration after hepatectomy, indicating that splenic factors suppress liver regeneration. Clinically, Sato et al. [10] found a negative association between liver regeneration and splenic volume in patients who underwent hepatectomy for hepatocellular carcinoma complicated by a chronic liver disorder. In the present study, the splenic volume before hepatectomy did not affect liver regeneration, probably because the subjects were jaundiced but had no cirrhosis. Without "splenomegaly," splenic factors may have little effect on liver regeneration after hepatectomy.

Conclusions

The spleen gains volume during liver regeneration, nearly doubling in size 1 month after major hepatectomy, but without further change. This increase in volume most likely represents regeneration of the spleen.

Résumé. On sait peu de choses sur le changement de volume de la rate pendant la régénération hépatique ou s'il y a un rapport entre les deux. Nous avons enregistré les changements progressifs des volumes spléniques et hépatiques par tomodensitométrie, chez 24 patients porteurs de cancer biliaire ayant eu une hépatectomie droite ou plus, après embolisation de la veine porte (EVP). Les segments non embolisés ont augmenté de volume de 316 ± -97 cm³ (34 ± 8% du volume hépatique total) avant EVP à 410 ± 114 cm³ (44 ± 8%) après EVP. Le volume des segments nonembolisés (foie restant) a augmenté de 617 ± 111 cm³ (59 ± 10%) du volume total avant EVP) 14 jours après hépatectomie et ensuite a augmenté progressivement à 795 ± 231 cm³ (76 ± 16%) à 1 an après l'hépatectomie. Le volume splénique a augmenté de 87 ± 29 cm³ avant EPV à 104 ± 38 cm³ (119 ± 17% du volume original) après EVP. Le volume splénique a augmenté à 137 ± 65 cm³ (155 ± 40%) à J 14 et à 155 ± 67 cm³ (179 ± 41%) à J 28 après l'hépatectomie, sans aucun changement à 1 an après l'hépatectomie (153 ± 92 cm³; 174 ± 79%). L'augmentation du volume splénique dans les 14 premiers jours après hépatectomie a été de 2.7 ± 3.6 cm³/jour, correspondant bien à celle du volume du foie restant (r = 0.64, p = 0.0006). Ces données indiquent que la rate augmente de volume pendant la régénération hépatique, suggérant que la rate et le foie partagent un certain nombre de mécanismes régulateurs de croissance.

Resumen. Poco se sabe sobre la relación existente entre la regeneración hepática y el tamaño del bazo. Mediante cortes seriados con tomografía computerizada estudiamos los cambios de volumen hepático y esplénico en 24 pacientes con cáncer biliar que sufrieron una hepatectomía derecha o una más amplia resección hepática tras embolización de la vena porta (PVE). El volumen de los segmentos hepáticos no embolizados aumentó desde 316 ± 97 cm³ (34 ± 8% del volumen hepático total) antes de la PVE, hasta 410 ± 115 cm³ (44 ± 8%) tras la PVE. El volumen de los segmentos hepáticos no embolizados (p.ej. el remanente hepático) aumentó hasta 617 ± 111 cm³ (59 ± 10% del volumen total del hígado antes de la PVE) a los 14 días de la hepatectomía y después siguió un lento incremento hasta alcanzar los 791 ± 231 cm³ (76 ± 16%) al año de la hepatectomía. El volumen esplénico aumentó desde 87 ± 29 cm³ antes de la PVE hasta 104 ± 38 cm³ (119 ± 17% del volumen original) tras la PVE. A los 14 días de la hepatectomía el volumen del bazo había aumentado 137 ± 65 cm³ (155 ± 40%) alcanzando los 155 ± 67 cm³ (179 ± 41%) a los 28 días de la hepatectomía; no se observaron más modificaciones del volumen al año de la hepatectomía (153 ± 92 cm³; 174% ± 79%). La tasa de incremento del volumen esplénico en los 14 días tras hepatectomía fue de 2.7 ± 3.6 cm³ /día, hecho que se correlaciona directamente con el incremento del volumen del remanente hepático (r = 0.64, p = 0.0006). Estos hallazgos indican que el bazo aumenta de tamaño durante la regeneración hepática, hecho que sugiere que el hígado y bazo tiene un mecanismo regulador común de crecimiento.

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特　集

肝切除・部分肝移植後の肝再生と肝不全―基礎と臨床―

5. 肝切除後肝不全の病態と対策―黄疸肝

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キーワード　肝不全，胆道癌，閉塞性黄疸，高ビリルビン血症，感染性合併症

I. 内容要旨

閉塞性黄疸を伴うことの多い胆道癌に対する広範囲肝切除では，術後に，感染性合併症や高ビリルビン血症が発症しやすく，それらがお互いに影響しあって肝不全が形成される．感染性合併症は，閉塞性黄疸による胆道感染，消化管の integrity の減弱，感染免疫能の低下などによって，また，高ビリルビン血症は，胆汁鬱滞に起因する肝細胞ミトコンドリア機能障害や胆汁成分の輸送蛋白の発現障害などによって発症すると考えられる．肝不全は一旦発症すると治療が困難であるので，閉塞性黄疸によって障害された肝，消化管，免疫などの予備能を十分回復させる術前処置を行うとともに感染症対策を講じることが重要である．

II. はじめに

閉塞性黄疸を伴うことの多い胆道癌に対する広範囲肝切除では，術後に，感染性合併症が発症しやすいこと，また，たとえ減黄後でも容易にビリルビンが上昇することが特徴であり，それらがお互いに増悪因子となって胆汁鬱滞性の肝不全が形成される（図1）．この点で，肝性昏睡，腹水，黄疸，出血などが主徴となる硬変肝に対する肝切除後肝不全とは若干その臨床像が異なる．

本稿では，かかる点から術後の血清総ビリルビン値10mg/dl以上の上昇を肝不全と定義し，閉塞性黄疸肝に対する肝切除術後の特徴，問題点，肝不全の予防策について概説する．

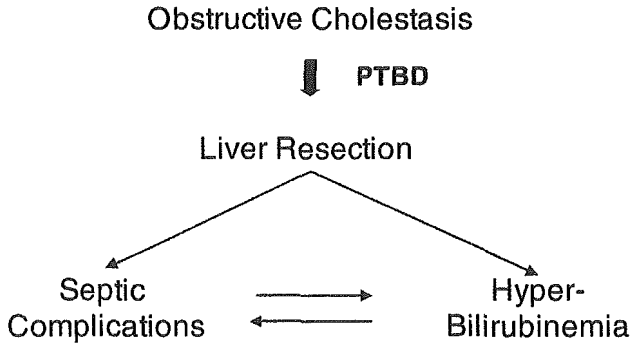

図1　閉塞性黄疸肝に対する肝切除の特徴

III. 閉塞性黄疸肝に対する肝切除後感染性合併症とその原因

胆道癌，特に閉塞性黄疸を伴っていた症例に対する肝切除後には，感染性合併症が多いことが特徴である．1992年からの10年間に教室で葉切除以上の肝切除を行った胆道癌症例（n＝232）の術後感染性合併症は，創感染，腹腔内膿瘍，菌血症などが多く，閉塞性黄疸のあった症例では，なかった症例に比べ，その発症が明らかに高率であった（図2）．このうち肝不全と密接に関連のある菌血症の発症を，10年間に行った全ての肝切除例（n＝407）で検討すると，肝細胞癌（n＝101）で4%，転移性肝癌（n＝62）で2%，良性疾患（n＝42）で1%であったのに対して，胆道癌（n＝200）では19%と有意に高率であった[1]．また，菌血症も含め，感染性合併症の起炎菌の多くは術前にPTBD胆汁中に高頻度に検

HEPATIC FAILURE FOLLOWING RESECTION OF CHOLESTATIC LIVER
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出される細菌であったことも，胆道癌肝切除例の特徴といえる．

本来，胆汁は無菌であるが，閉塞性黄疸患者ではしばしば胆汁中に細菌が証明される．閉塞性黄疸肝に対する肝切除後になぜ菌血症がおこりやすいのかはよくわかっていない．しかし，検出される菌の種類から，胆汁や腸管内の細菌が直接・間接に血流に入っていることはほぼ間違いない．胆管閉塞による肝細胞の tight junction の異常により胆汁中細菌が直接門脈血流に移行する可能性が示唆されている[2]．また，閉塞性黄疸による腸管内胆汁の長期にわたる欠如や，手術侵襲による腸管の透過性の亢進によって腸内細菌が門脈血流へ移行（bacterial translocation）しやすくなることも知られている[3]．実際，教室での臨床例の検討によって，胆汁外瘻では消化管の透過性が亢進するものの，外瘻胆汁の消化管への返還によって透過性が正常に回復することが証明されている[4]．大量肝切除により人体最大の網内系臓器を切除すること，黄疸肝における Kupffer 細胞の機能低下なども，菌血症が発生しやすい原因となりうると考えられる．さらに，黄疸肝の感染抵抗性の低下については，肝細胞アポトーシスによって誘導された Kupffer 細胞の IL-10 産生亢進がその原因の1つであることをわれわれは見いだしている[5]．

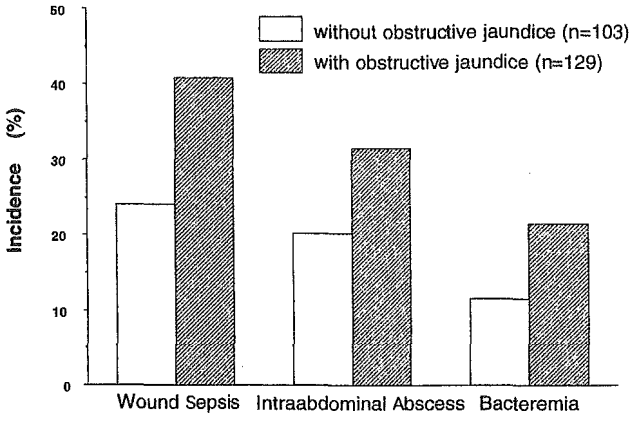

図2　胆道癌に対する広範囲肝切除例の感染性合併症発症率（1992–2002）

IV. 閉塞性黄疸肝に対する肝切除後高ビリルビン血症とそのメカニズム

教室では，肝切除が予定される胆道癌による閉塞性黄疸患者では，全例減黄後に手術を行っている．1992年からの10年間に葉切除以上の肝切除を行った胆道癌232例（胆管癌152例，胆嚢癌60例，胆管細胞癌20例）の検討では，入院時に黄疸を伴っていた症例（n＝137）の術後の最高血清ビリルビン値の平均は，10.1±11.3mg/dl で，非黄疸例（n＝95）の 6.5±5.9mg/dl に比べて有意に高値であった．また，血清ビリルビン値の10mg/dl 以上の上昇を肝不全と定義すると，肝不全発生率は入院時非黄疸例で 17.1%，有黄疸例で 23.7% であり，閉塞性黄疸を伴っていた症例に肝不全の発症が高率であった．

閉塞性黄疸時には，肝細胞ミトコンドリアの酸化的

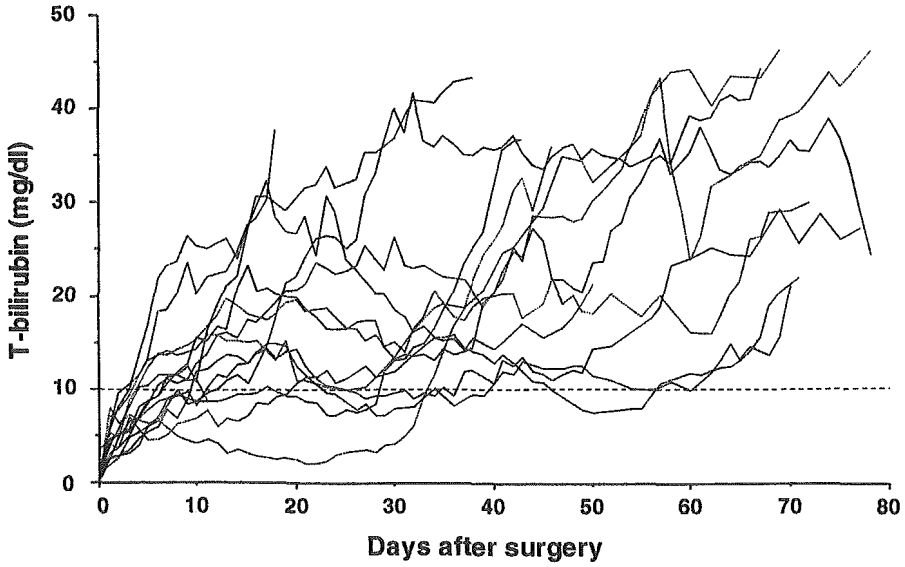

図3　肝不全死亡例の術後血清ビリルビン値の推移（n＝13，1995–1999）

リン酸化能が障害されていることが知られており，uncouplerとしてのビリルビン[6]，界面活性剤としての胆汁酸[7]がその原因物質として推定されている．また，胆汁鬱滞に胆管炎が加わると，減黄後もミトコンドリア機能の障害が遷延することが知られている[8]．ミトコンドリアによるATPの産生低下は，肝細胞における合成・抱合などの代謝に影響を及ぼすのみならず，ビリルビンのような有機陰イオンや胆汁酸の肝細胞への取り込み，毛細胆管への排泄など，ATPに依存した能動輸送をも低下させる．さらに，胆管閉塞あるいはそれに炎症（胆管炎）が加わると，抱合型ビリルビンの排泄に必要不可欠なmultidrug resistance protein 2(MRP2)の肝細胞毛細胆管膜での発現が減少することが動物実験によって証明されている[9]．教室における胆道癌肝切除例の検討(n＝39)では，手術開腹時の予定残存肝のMRP 2蛋白の発現が不良な6症例のうち4例に肝不全が発生していた．すなわち，胆管閉塞によって障害されたMRP 2の発現がPTBDを行っても回復しない症例で，術後の高ビリルビン血症が発生しやすいといえる．

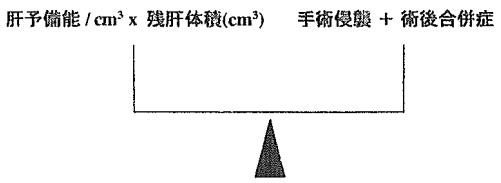

図4　肝不全発症のメカニズム

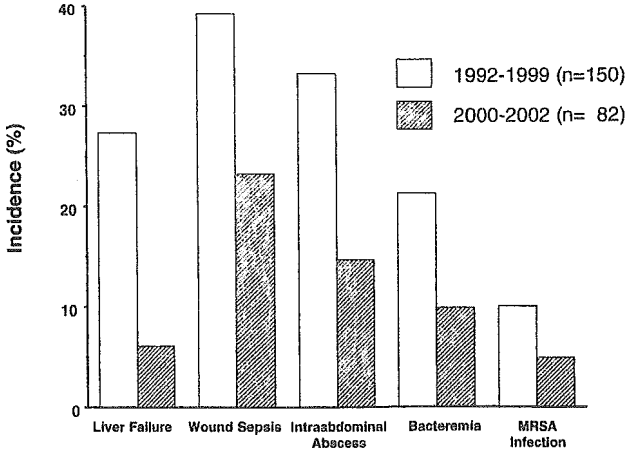

図5　胆道癌に対する広範囲肝切除後の肝不全と感染性合併症の時代的推移

V. 閉塞性黄疸肝に対する肝切除後肝不全の病態と肝不全対策

前述のように，胆道癌などにより閉塞性黄疸を経験した肝臓は，胆汁排泄能が障害されており，また感染抵抗性が減弱している．肝不全の発症には感染が契機となることが多く，逆に肝不全は感染性合併症を増悪させる[10]．胆道癌肝切除後肝不全の特徴を明らかにするため，1995年からの5年間に経験した肝不全死亡例の術後の血清ビリルビンの推移を図3に示した．大きく分けると，術直後からビリルビンが急上昇する症例と，ビリルビンが比較的低値をさまよった後ある時を契機に急上昇する症例が存在する．前者の多くは肝機能に対して切除量が多すぎたと推定される．後者も同様であるが，ビリルビンの急上昇の契機の多くが感染性合併症であることが注目される．これらの事実は，術後の合併症を含めた手術侵襲と残肝機能とのバランスによって肝不全が発症することが示唆している（図4）．すなわち，胆道癌など閉塞性黄疸を経験した肝臓に対する肝切除では，ある程度の割合で感染性合併症が起こることは避けられないので，それが起こっても耐術できるように，術前から肝予備能を高めたり，腸管のintegrityを保っておく術前処置が必要であり，逆に肝機能不良例には，十分な残肝体積を確保する手術術式を選択する必要がある．

現在，黄疸肝の肝予備能を評価する適切な方法は存在しないといえる．教室では，全胆道がドレナージされている場合には，残肝KICG値(KICG×予定残肝率)≧0.05を耐術のおおよその目安にしているが，全肝がドレナージされていない場合の評価方法については確立していないのが現状である．

前述のごとく，肝不全対策と感染症対策は表裏一体であることから，教室では以下のような肝不全対策を行っている．

＜術前・術後の胆汁返還＞術前・術後を通じて，PTBD胆汁はその全量を経口あるいは経管的に腸管に戻す．これは，腸粘膜の保護[4]と，それによるbacterial translocationの予防，胆汁酸の腸肝循環の維持による肝機能の回復に役立つ．胆汁内瘻は肝切除後の肝再生に有用であり[11]，また胆汁酸の腸肝循環によって抗生剤の胆汁移行が改善するとの報告[12]がある．

＜経皮経肝門脈枝塞栓術（PTPE）＞肝右葉以上の切除が予定されれば，PTPEを行う[13]．PTPEにより，肝切除率を10%程度低下させることができ，また，残存

予定肝の胆汁排泄能を術前に高めておくことができる[14].

＜区域性胆管炎の治療＞肝門部胆管癌など肝門部で区域あるいは亜区域胆管枝が分断されているような症例では，PTBDがなされていても，必ずしも全ての胆管枝がドレナージされているわけではない．区域性胆管炎を疑う症状があれば漫然と抗生剤を投与するのではなく，速やかにCTなどで拡張した区域・亜区域胆管枝の存在を診断し，緊急に選択的PTBDを追加する[15].

＜術中の胆道減圧および胆汁による術野の汚染の予防＞手術中も胆道減圧には注意を払い，また，PTBD胆汁は無菌的に手術野で管理し，胆汁による腹腔内の汚染を防ぐ．

＜術中・術後の抗生剤の選択＞肝切除後の感染性合併症の起炎菌の多くが胆汁中細菌に一致するので，術前にPTBD胆汁中の細菌の同定と抗生剤の感受性試験を行い，術中・術後に使用する抗生剤を術前に選択しておく．

VI. おわりに

胆道癌広範囲肝切除例では，閉塞性黄疸に起因する免疫能の低下，術前の胆道感染率の高さ，手術侵襲の大きさなどから，術後の感染性合併症はある程度発症するものと認識するべきである．感染性合併症が発症しても耐術できるように，肝・消化管の機能を術前に高めておくことが重要である．教室では，これらの肝不全対策が徹底した2000年以後，胆道癌肝切除後の肝不全，感染症は大きく減少した(図5)．同じ頃より，非加熱血液製剤の使用を極力控えるようにしたことも，肝不全の発症低下に貢献していると推定している．

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HEPATIC FAILURE FOLLOWING RESECTION OF CHOLESTATIC LIVER

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Hepatectomy for biliary cancer with obstructive jaundice is often followed by postoperative septic complications associated with hyperbilirubinemia, both of which could lead to cholestatic liver failure by affecting each other. Such septic complications seem to develop from contamination of bile, reduction of intestinal integrity, or impairment of host resistance to bacteria, each resulting from biliary obstruction. Hyperbilirubinemia after hepatectomy is demonstrated to develop due to hepatic mitochondrial dysfunction or impaired expression of bile efflux pumps on the canalicular membrane of hepatocytes. Since no therapeutic strategy is established for liver failure following hepatectomy, it is important to take all possible measures before surgery to enhance the functions of the liver, intestine, and host immunity and to prevent postoperative septic complications.

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特　集

腹部外科領域における interventional radiology の応用：最新の知見

2. 広範囲肝切除術に対する経皮経肝門脈枝塞栓術（PTPE）の有用性

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キーワード　経皮経肝門脈枝塞栓術（PTPE），肝再生，術後肝不全

I. 内容要旨

局所進行胆道癌では広範囲肝切除を必要とすることが多く，周辺臓器の合併切除を要する症例も少なくない．かかる症例に対し術後肝不全を回避するために経皮経肝門脈枝塞栓術（PTPE）は有効である．PTPEにより予定残肝体積率は右葉，右三区域塞栓術で約10%，左三区域塞栓術で約7%増加した．PTPEの導入により広範囲肝切除後の肝不全発症率，在院死亡率はそれぞれ33.3%から23.8%，21.9%から9.5%に減少したが，成績は未だ満足すべきものではなく，安全性向上のために更なる努力が必要である．

II. はじめに

局所進行胆道癌の外科的治療は広範囲肝切除に加え，肝動脈，門脈，十二指腸など周辺臓器の合併切除を併施することにより根治切除ができる機会がますます増えてきた[1]．その一方でかかる過大な侵襲により術後合併症から死亡にいたる症例はいまだ少なくない[2]．広範囲肝切除で最も重篤な合併症は術後肝不全であり，これを回避するため術前に残肝予備能を高めておくことが重要である．

Makuuchi[3]，Kinoshita[4]らにより臨床応用された門脈枝塞栓術は肝臓を「小さくとって大きく残す」ことを可能にした画期的な手技である．それは経皮経肝アプローチ(PTPE)[5]によりどこの施設でも低侵襲かつ簡便に行えるようになった．PTPEの導入により術後肝不全の発症率が減少したばかりか，残肝機能が憂慮される症例に対しても広範囲肝切除が可能にり，切除率が向上した．

われわれは広範囲肝切除（尾状葉切除を伴う肝右葉切除，拡大右葉切除，右三区域切除，左三区域切除）が予定される患者に対しPTPEを施行し，これまでにその症例数は150例に達した．本稿では当教室におけるPTPEの成績とその有用性について最新の知見をまじえながら紹介する．

III. 対象と方法

対象は1991年から2003年までに教室でPTPEの後，肝切除を施行した胆道癌症例147例である（Table 1）．動脈塞栓術（TAE）とPTPEを併施した3例は除外した．閉塞性黄疸のある症例では全例減黄術を行い，血清総ビリルビン値が2.0mg/dl前後に減黄された後にPTPEを施行した．塞栓した肝区域は右葉106例，右三区域22例，左三区域19例で，2000年12月までの症例は塞栓物質としてfibrin glueを用い，2001年1月からは無水エタノールとコイルを用いて塞栓術を施行した．肝の体積はCT volumetry，肝機能はICG排泄率(K_{ICG})を用い評価した．PTPE後，CT再検までの期間は15.9±10.0日（中央値14日，最大値109日，最小値6日）で

BENEFIT OF PERCUTANEOUS TRANSHEPATIC PORTAL VEIN EMBOLIZATION FOR EXTENDED HEPATECTOMY

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Table 1 対象疾患と塞栓区域

	(n=147)
疾患	
肝門部胆管癌	85
胆嚢癌	50
胆管細胞癌	10
原発性硬化性胆管炎	2
塞栓区域	
右葉塞栓	106
右3区域塞栓	22
左3区域塞栓	19

あった．手技に伴う合併症として一過性の肝逸脱酵素の上昇，微熱，hemobilia を認める症例があったが全例保存的に軽快した．

IV. PTPE による塞栓葉と非塞栓葉の体積変化

PTPE により塞栓葉，非塞栓葉それぞれで門脈血流の変化とそれに伴う肝動脈血流の変化が起きるが[6]，血流の変化がどのようにシグナル伝達されて静止期の肝細胞を regeneration あるいは apoptosis に誘導するのかは明らかでない．しかし，PTPE により塞栓葉で萎縮した体積とほぼ同じ体積が非塞栓葉で増加する（Volume の移動）．自験例では PTPE 前後の尾状葉を除く塞栓葉/非塞栓葉の体積（肝全体に占める体積比率）の変化は右葉塞栓術で 668±146cm^3（62.3±6.6%）/366±104cm^3（33.9±6.4%）から 556±124cm^3（52.0±6.6%）/468±108 cm^3（43.8±6.5%），右3区域塞栓術で 800±168cm^3（74.0±5.9%）/245±71cm^3（22.8±5.4%）から 719±161 cm^3（64.2±6.0%）/356±74cm^3（32.3±5.6%），左3区域塞栓術で 735±203cm^3（60.8±8.6%）/437±153cm^3（35.9±8.1%）から 644±160cm^3（53.3±8.0%）/528±166 cm^3（43.0±7.4%）で右葉，右3区域塞栓術ではおよそ 10%，左3区域塞栓術ではおよそ 7% の volume の移動が起こったことになる（Fig. 1）．自験例では平均 K_{ICG} が 0.152 であったが，Kubo らは平均 ICG 15 分値 13.3%（K_{ICG} 0.13 相当）の肝細胞癌症例に対し右葉塞栓術を行い，残肝増加率が平均 7.8% であったと報告している[7]．自験例の多くは減黄術後に PTPE を施行しているので単純比較はできないが，慢性肝炎，肝硬変を伴う症例では PTPE 後の残肝増加率は低いと思われる．糖尿病を合併している症例でもその増加率は低い[8][9]．また，女性の耐術能力の高さは経験から知りうるところであるが，その理由のひとつとして estrogen が肝再生を促進すると考えられており[10]，女性が肝再生に有利な環境にあることがあげられる．右葉塞栓術で比較すると女性，男性の増加率がそれぞれ 10.8±3.9% と 9.2±4.0% で有為に女性の残肝増加率が高かった（$P<0.05$）．これは Imamura ら[9]の報告を支持する結果である．自験例には post-menoposal な患者も相当数含んでおり estrogen だけにその理由を求めることはできないが，そのメカニズムの解明によりさらに効果的な PTPE が可能になると思われる．

ここで疑問となるのが，果たして予定残肝 volume の増加がそのまま function の増加につながっているかという点である．われわれは以前，肝門部胆管癌症例で塞栓葉，非塞栓葉に別々にドレナージカテーテルが挿入された症例に ICG 検査を行い，PTPE 前後で残肝体積の増加（平均 8.3%）とともに胆汁中 ICG 排泄量が増加（平均 20.1%）することを示した[11]．また，最近では viable な肝臓に特異的に結合する ^{99m}Tc で標識した galactocyl human serum albumin（GSA）を用い PTPE 前後でその吸着率が 30% 増加することが報告されている[7]．予定残肝の肝機能を正確に定量することは困難だが，上記の結果から volume の増加と同等，もしくはそれ以上に function の増加が起こると考えてもよいだろう．

V. 術後肝不全の予防の手段としての PTPE の有効性

PTPE の導入により広範囲肝切除の安全性が着実に増した．近年肝動脈，門脈，膵頭十二指腸合併切除を併施した広範囲肝切除術など侵襲の大きい手術が増えているにもかかわらず，PTPE 導入前に広範囲肝切除を施行した 64 例では術後肝不全（血清総ビリルビン値>10 mg/dl）が 21 例（33.3%），在院死亡が 14 例（21.9%）であったのに対し，PTPE 導入後ではそれぞれ 35 例（23.8%），14 例（9.5%）とその発生頻度は減少している．

われわれは広範囲肝切除術に対する耐術の指標として残肝 K_{ICG}（K_{ICG}×予定残肝率）が 0.05 以上を目安にしている．残肝 K_{ICG} 値が 0.05 以上であった 121 例における術後肝不全症例は 22 例（18.2%），肝不全から死亡にいたった症例 8 例（6.6%）であったのに対し，0.05 未満であった 26 例ではそれぞれ 11 例（42.3%），6 例（23.1%）と高率であった（Fig. 2）．減黄された肝臓が肝機能を回復するまでの時間には time lag があり[12]，残

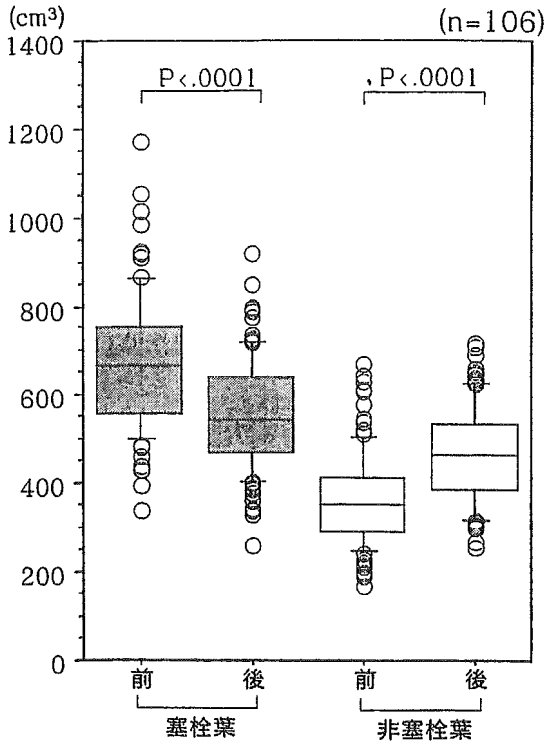

Fig. 1a　右葉塞栓術後の体積変化

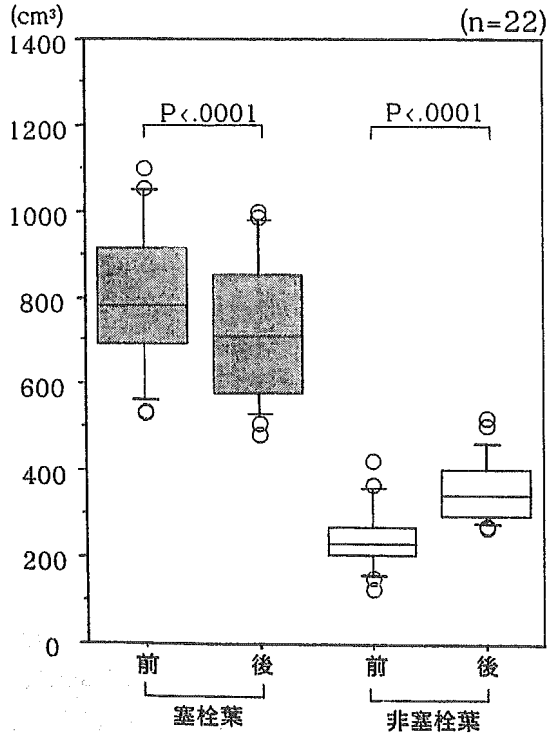

Fig. 1b　右3区域塞栓術後の体積変化

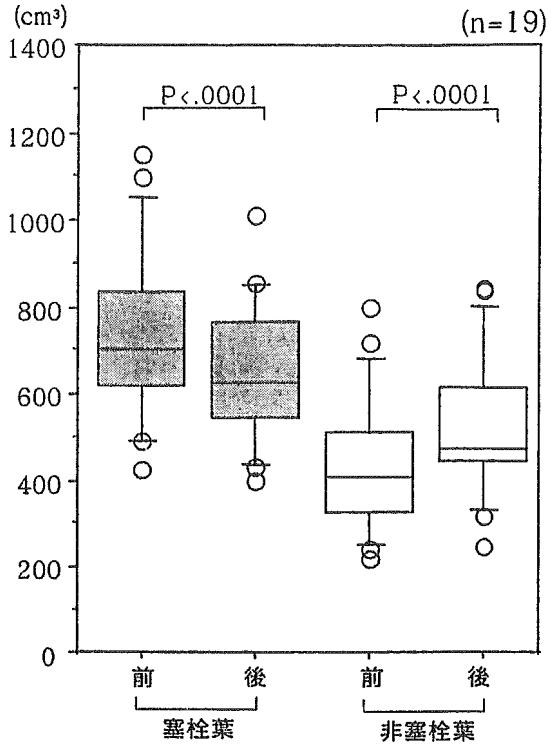

Fig. 1c　左3区域塞栓術後の体積変化

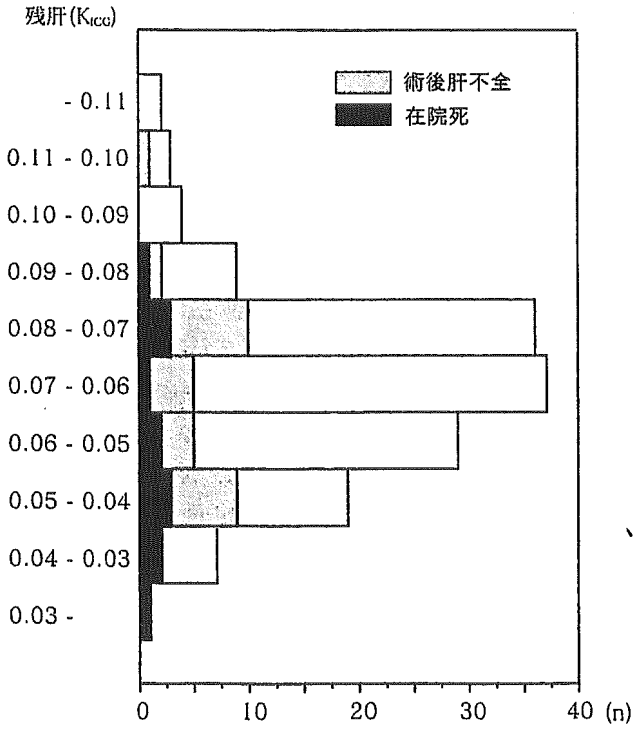

Fig. 2　残肝 K_{ICG} と術後肝不全発生頻度

肝 K_{ICG} 値を単純比較することはできないが，PTPE により残肝 K_{ICG} 値は 0.051±0.014 から 0.068±0.016 に増加しており，肝不全回避のために PTPE は有効であったと言えよう．

また，PTPEの導入が手術術式に及ぼした影響も大きい．PTPEにより肝切除の安全性が増し，safety marginが十分にとれる広範囲肝切除の選択が可能になった．肝門部胆管癌症例に限ると，教室で切除した265例中，尾状葉単独切除あるいは中央2区域＋尾状葉切除，前区域切除＋尾状葉切除などの肝の中央を切除する術式を選択した症例はPTPE導入前が75例中15例(20.0%)であったのに対し，導入後は190例中13例(6.8%)であり，広範囲肝切除術が選択される頻度が増えてきている．

VI. 塞栓物質の違いによるPTPEの効果の相違：fibrin glue vs エタノール

PTPEで使用される塞栓物質にはスポンゼル[3][9]，fibrin glue[5][7]，無水エタノール[13][14]，cyanoacrylate[15]などがある．われわれは当初バルーン付きdouble lumenカテーテルを用いてfibrin glueを門脈枝内に注入し塞栓を行ってきた．fibrin glueは組織反応性，刺激性がほとんどなく，注入に伴う痛みがないため患者に強いる負担は少ない．しかし，fibrin glueは高価で，数年前より保険請求ができなくなった．そこで現在はfibrin glueに比べ安価な無水エタノールと血管塞栓用のコイルを併用することによりPTPEを行っている．自験例でその塞栓効果を右葉塞栓術で比較すると，fibrin glueを用いた73例で非塞栓葉の増加率は10.2±4.0%に対し，エタノールを用いた23例は9.4±4.0%で有意差を認めなかった．しかし，報告例をみるとTAIの併用やPTPE後のfollow up期間がまちまちで単純比較はできないが，概ねエタノールを使用した方がその増加率はいいようである[13][14]．エタノールによる塞栓術はそのメカニズムから推察させるように再疎通率は低く，fibrin glueが108例中9例（8.3%）に対しエタノールでは39例中2例（5.1%）であった．しかし，エタノールがもつ刺激性から注入に伴う疼痛が問題となる．われわれは注入の直前にミタゾラムを静注し，意識levelを落とした上でPTPEを行っている．

VII. PTPEに伴う肝再生

肝再生のメカニズムに関する研究は多数あるが，いまだ十分な答えが得られていない．どのような刺激が再生のtriggerとなり，何が肝臓のvolumeを規定（再生のendpointの決定）しているのかは，研究者ならずとも興味を引くところである．通常の肝再生は肝切除後あるいはウィルス性肝障害後のように肝体積の減少（肝細胞数の減少）が先行し再生が起こるのに対し，門脈塞栓術後の肝再生は門脈血流の変化をうけ肝の萎縮と再生がほぼ同時に起こる点で異なっている．われわれはPTPEに伴う肝再生はそのメカニズムを解明するうえで新しい手段となりうると考えている．これまでsurgical stressや腸管からのbacterial translocationなどの刺激でKuppfer cellsから分泌されるpro-inflammatory cytokine（TNF-α，IL-6）が肝再生のtriggerと考えられてきたが[16][17]，PTPEは局麻下に行う手技で，surgical stressなどの影響はほとんど無視できる．PTPE後の肝再生を検証することにより，他の因子に影響されない肝再生固有のメカニズムが解明できると考えている．われわれは門脈血流の増加そのものが再生刺激となっていると考え，超音波ドップラーを用いPTPE直後の門脈血流の増加率に比例して再生速度が増すことを報告した[18]．また，門脈血流の増加にともない血管内皮細胞に機械伸展刺激が加わることに注目し，*in vitro*で牽引強度依存性にIL-6が分泌されることを実験的に証明した[19][20]．現在，ratを用いPTPEモデルを作成し，surgical stressの影響のない肝再生のメカニズムについて研究を進めている．そのメカニズムを解明することによりPTPEの再生効率を上げ，広範囲肝切除の安全性をさらに高めることが今後の課題であると考えている．

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