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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Long-term results of major bile duct injury associated with laparoscopic cholecystectomy

C. S. Huang, H. H. Lein, F. C. Tai, C. H. Wu

Department of Surgery, Cathay General Hospital, Taipei Medical University, Taipei, Taiwan

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Abstract
Background: Major bile duct injury (MBDI) is the most serious complication associated with laparoscopic cholecystectomy (LC). This study reports on long-term outcomes and clinical factors which predicted the outcome of 25 patients with LC-associated MBDI.
Methods: Twenty-five consecutive patients receiving either primary ($n = 11$) or redo ($n = 14$) biliary reconstructive surgery at Cathay General Hospital for LC-associated MBDI were prospectively followed for 2 to 10 (mean, 4.5) years to assess their long-term outcomes. Twelve clinical factors relevant to their outcomes were analyzed.
Results: There was no mortality. Although the 1-year postoperative results were successful in 23 patients (92%), the mid- to long-term outcomes were successful in only 17 patients (68%). Eight patients (32%) developed biliary strictures at an average of 3.3 years postoperatively and required subsequent reoperation or biliary stenting. Statistical comparison of 12 risk factors between the successful and unsuccessful groups revealed that two were significant, namely, repair performed by a nonreferral surgeon ($p = 0.02$) and repair at a stage with recent active inflammation ($p = 0.04$). A serum alkaline phosphatase level greater than 400 IU in the sixth postoperative month was highly correlated with long-term nonsuccess ($p = 0.01$).
Conclusions: Only 68% of patients with LC-associated MBDI who underwent reconstructive surgery at our institution had long-term success. A serum alkaline phosphatase level above 400 IU in the sixth postoperative month was predictive of nonsuccess. For better long-term results, repair should be performed by the referral surgeon at a stage without coexisting active inflammation.

Key words: Bile duct injury — Laparoscopic cholecystectomy — Biliary stricture

Correspondence to: C. S. Huang

Iatrogenic bile duct injury is one of the most serious complications associated with laparoscopic cholecystectomy (LC). Bile duct injury occurs with a higher incidence and at a higher level on the proximal bile duct with LC than with open cholecystectomy [1, 5, 12, 13]. Minor injuries (Strasberg classes A to D) [13] can be managed with either therapeutic endoscopy or interventional radiology, even when various surgical repairs are necessary; the results are usually satisfactory without long-term sequelae [8, 14]. On the other hand, management of major bile duct injuries (MBDIs, Strasberg classes E_1 to E_4, Table 1) [13] is always surgical once the bile duct is completely transected with ductal tissue loss; surgical repairs for these patients are more difficult and complicated [2, 9]. Furthermore, biliary reconstructive surgery is also indicated for those patients who develop postoperative biliary stricture after primary repair for an MBDI when the stricture cannot be relieved by nonsurgical treatment. Although short-term results of reconstructive surgery for MBDI were reported with success rates ranging from 75% to 86% [3, 11], the reconstructed biliary tract has a tendency to cicatrize and become restenotic at the anastomosis. Therefore, long-term results may not be as good as short-term ones. Only a few reports have mentioned long-term results [6, 7]. The purposes of this study were to present the mid- to long-term results of 25 patients with LC-associated MBDI who had received reconstructive surgery at our institution over a 9-year period and to analyze the clinical risk factors influencing the long-term results.

Materials and methods

Twenty-five consecutive patients who underwent primary ($n = 11$) or redo ($n = 14$) biliary reconstructive surgery at Cathay General Hospital from December 1990 to December 1998 for LC-associated MBDI (Strasberg classes E_1 to E_4; Fig. 1) were prospectively followed for from 2 to 10 years. Patients with minor injuries (Strasberg classes A to D) were excluded from this study because of their relative benign clinical courses. The primary repair group included six patients who sustained an MBDI from our own 3500 LC before 1998 and five patients who were referred to us after sustaining an MBDI in other

Table 1. Level of injury or stricture in 25 patients with major bile duct injury repaired at Cathay General Hospital (1990–1998)

Strasberg class[a]	E_1	E_2	E_3	E_4
Primary (n = 11)	2	6	3	0
Redo (n = 14)	1	5	2	6
Total (n = 25)	3	11	5	6

[a] Strasberg classification: type E injury is circumferential injury or stricture involving main bile duct; E_1: transection or stricture at more than 2 cm below hepatic confluence; E_2: less than 2 cm below confluence; E_3: confluence is preserved but there is no residual common hepatic duct; E_4: confluence destroyed

hospitals. The average time interval between the bile duct injury and biliary reconstruction for the 11 primary repair patients was 24 (range, 0–121) days. All 14 patients in the redo group were referred from other hospitals, and the average time interval between primary repair and the redo operation for these patients was 33 (range, 4–108) months. There were 13 male and 12 female patients, aged from 23 to 80 (avg 54.4 ± 15.8) years. Eight of the 25 patients presented with concomitant active inflammation in the same admition for reconstructive surgery.

In detail, among 11 patients in primary group four had concomitant active inflammation (biloma with or without bile drainage through subhepatic drain: 3; subhepatic abscess with obstructive jaundice: 1), all these four patients had fever, leukocytosis (16–27 × 10^3) and positive blood culture (*Escherichia coli:* 2 *Serratia marcescens:* 1, *Klebsiella pneumoniae:* 1). Among 14 patients in the redo group, four had concomitant active inflammation of acute suppurative cholangitis with fever, leukocytosis, and positive blood culture (*E. coli:* 2, *K. pneumoniae:* 1, *Sternotrophomonas maltophilia:* 1); one of them had multiple liver abscess.

The concomitant infections were treated first with antibiotics and percutaneous drainage procedures before bile duct reconstruction. Except for the four patients with MBDI who were immediately converted to open surgery and who received primary repair of their CBD transections, all of the remaining 21 patients had preoperative image studies to confirm the presence and exact location of their LC-associated MBDI (n = 7) or delayed strictures (n = 14). The image studies included endoscopic retrograde cholangiopancreatography (ERCP, n = 12), percutaneous transhepatic cholangiography (PTC, n = 1 4), magnetic resonance cholangiopancreatography (MRCP, n = 2), and HIDA scan (n = 2). Among them, any one patient might have more than one kind of image study. Additional intraoperative cholangiography was also used to delineate the biliary anatomy during repair in three patients. Table 1 shows the distribution of the levels of bile duct injury or stricture according to Strasberg's classification. The redo group had higher levels of injury than the primary repair group. None of the patients in the primary repair group received therapeutic endoscopy or therapeutic radiological procedure due to their circumferential injury and tissue loss of major bile duct. Among the 14 patients who received redo operations for biliary stricture, eight had received therapeutic endoscopic or radiology-guided dilatation and stenting attempts before being referred to us, but these attempts at management eventually failed to release the bile stasis and the cholangitis. The dilatation and stenting procedures included endoscopic retrograde dilatation and stenting in three patients on their previous primary anastomosis over T-tube, and radiology-guided dilatation through PTCD tract with or without temporary stents in five patients on previous RY anastomosis. The remaining six patients in the redo group with biliary stricture received straightforward redo operations due to apparent rigid and long-segment stenosis (Fig. 2). The biliary reconstructive procedures performed on the 25 patients and the types of previous repair procedures for the 14 redo patients are shown in Table 2. Except for one patient on whom we performed direct repair over the T-tube as the primary repair, all patients received a Roux-en-Y biliary-enteric anastomosis as the reconstructive procedure. Five of the 11 primary repairs were performed by the same surgeons who had transected the CBD during LC. The remaining six primary repairs and all of the 14 redo operations were performed by two senior staff surgeons. Postoperatively, all patients were followed up at a special clinic according to a protocol designed for bile duct injuries. Clinical

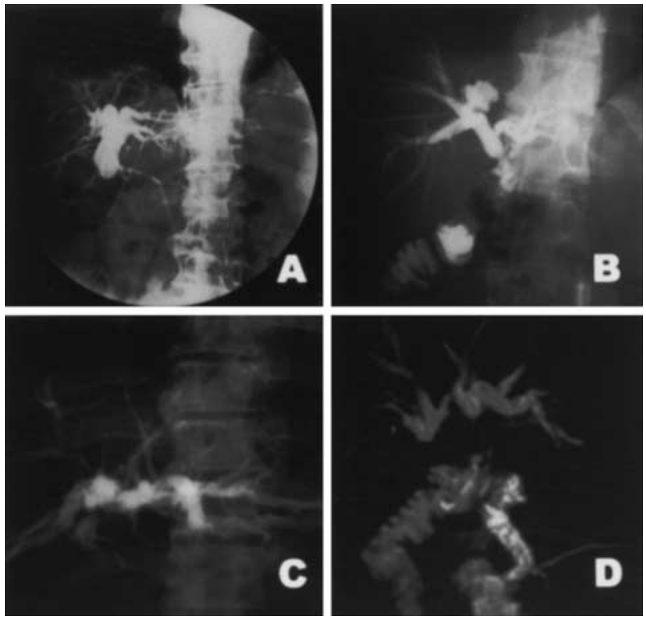


Fig. 1. Examples of patient's percutaneous transhepatic cholangiogram (**A, B, C**) and MRCP (**D**) showing Strasberg classes E_1 (**A**), E_2 (**B**), E_3 (**C**), and E_4 (**D**) major bile duct injury.

symptoms, blood cell counts, abdominal sonography, and liver enzymes were checked routinely in the first, sixth, and 12th postoperative months, and then annually. Additional examinations such as MRCP, CT, and HIDA scans were performed if biliary symptoms developed or elevated liver enzymes were found. However, a definite diagnosis of postoperative biliary stricture depended on positive findings of PTC examination among patients with RY anastmosis and ERC examination among patients with direct duct repair. Subsequent endoscopic or radiological dilatation-stenting procedures, or further redo surgery were regarded as the end point of follow-up. Patients who received these therapeutic interventions were classified as unsuccessful. Twelve risk factors including patient age, gender, operating time, primary versus redo operation, timing of repair, direct repair over T-tube as previous repair, level of injury, preoperative serum alkaline phosphatase level higher than 400 IU (Alk P; normal range for Taiwanese adults: 60–205 IU/L), repair by primary (nonreferral) surgeon, perioperative active inflammation (cholangitis, intraabdominal abscess, or biloma with accompanying leukocytosis and fever), presence of subhepatic or transhepatic biliary drainage for more than 2 months, and the use of stenting across the anastomosis were compared between the successful and unsuccessful groups. Postoperative mean serum Alk P levels of the successful and unsuccessful groups at designated time points of follow-up and their trends were also compared. The age and operating time are expressed as the mean ± SD. Other risk factors are expressed as the absolute number of patients presenting the risk factors. For data analysis and statistics, the PC-based software SPSS for Windows (SPSS Inc., Chicago, IL, USA) was generally applied. The t-test was used to test differences of average age, average operating time, and area-under-the-curve of the postoperative serial serum Alk P level between the successful and unsuccessful groups. Mann–Whitney rank sum tests were used to test the significant impact of timing of surgery and the level of injury or stricture on the long-term results. All other variables were examined with Fisher's exact text for statistical significance (a p value of less than 0.05 was chosen as the limit of significance).

Results

Follow-up periods ranged from 2 to 10 (mean, 5.1; median, 6) years. There were no deaths, and none of the 25 patients was lost during the follow-up period. Re-

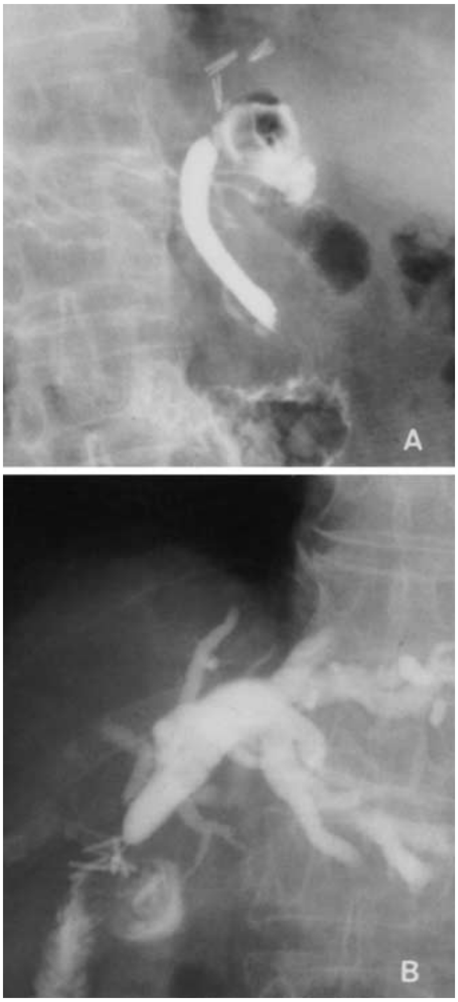


Fig. 2. Examples of patient's ERCP (**A**) and PTC (**B**) showing apparent long-segment (**A**) and rigid (**B**) biliary stenosis.

peated cholangitis with image-proven restenosis which required further interventional procedures was observed in two patients during the first postoperative year; however, image-proven restenosis with repeated cholangitis was observed in six additional patients as the follow-up period increased. Figure 3 shows the mid- to long-term event-free survival in the 25 patients according to life table model. Seventeen patients (68%) were classified as long-term successes, including 13 patients who were free of symptoms with normal liver enzymes for all time points of the postoperative follow-up and four patients who had transient cholangitis which was easily controlled with fluid and antibiotic therapy without interventional procedures, yet remained asymptomatic for at least 2 years, while their imaging studies revealed no postoperative biliary stasis. The results of the remaining eight patients (32%) were classified as unsuccessful because all of them suffered from repeated episodes of cholangitis either in the immediate postoperative period or after a certain period of initial success. Because of the severity of clinical symptoms and image-proven biliary stricture, five of them required subsequent endoscopic or radiological dilatation with stenting, while the other three patients required an ultimate reoperation at an average of 3.3 years after biliary reconstruction.

The impact of risk factors on the mid- to long-term outcomes

Table 3 shows the presence of 12 risk factors which were considered to have potential influences on long-term patient outcomes in the successful and unsuccessful groups. In the primary repair group ($n = 11$), nonreferral surgeons repaired five MBDIs, with only one long-term success, while referral experienced surgeons repaired six with five successes. In the redo group ($n = 14$), all patients were repaired by an experienced referral surgeon; 11 patients had long-term success. Trends of postoperative mean serum Alk P levels for the successful group and the unsuccessful group are shown in Fig. 4. The individual p values for each risk factor are shown in the last column of Table 3. Univariate analysis revealed that significant risk factors included repair performed by a nonreferral surgeon ($p = 0.02$) and perioperative active inflammation ($p = 0.04$). A serum Alk P level greater than 400 IU in the sixth postoperative month showed a high correlation ($p = 0.01$) with long-term nonsuccess. Further subdivision of the presence of risk factors in the primary repair group and the redo group is also shown in Table 3. Statistical analyses for the subgroups were not performed because of the small sample size of the subgroups.

Discussion

This mid- to long-term follow-up of 25 patients, who had received primary or redo biliary reconstructive surgery for LC-associated MBDI at Cathay General Hospital from 1990 to 1998, revealed successful outcomes in only 17 patients (68%). The remaining eight patients (32%) were subjected to further therapeutic endoscopic, radiological procedures ($n = 5$), or redo surgery ($n = 3$) for their postoperative biliary stricture with cholangitis at an average of 3.3 years after reconstructive surgery. The eight patients with unsuccessful outcomes had initial postoperative Alk P levels comparable to those of the successful group. However, subsequent Alk P measurements for the unsuccessful group continued to rise while the values for the successful group were gradually declining. A serum Alk P level greater than 400 IU in the sixth postoperative month or beyond had a high correlation ($p = 0.01$) with long-term restenosis. This suggests that anastomotic cicatrization gradually developed postoperatively. The cicatrization reached an irreversible stage of stricture as early as the sixth postoperative month. This finding is consistent with Schol et al.'s report of an average time lapse of 134 days between repair and restenosis [11]. Compared to the 90% long-term successes in the study of Murr et al. [6], our results are less favorable. This may be due to different compositions and follow-up periods of the two study groups, as our study included MBDI (Strasberg classes E_1–E_4) only, 14 out of the 25 repairs

Table 2. Reconstructive procedures for the 25 patients with major bile duct injury at Cathay General Hospital (1990–1998)

	No. of patients	Stratsberg's classification
Primary repair ($n = 11$)		
PT[a]	1	E_1 (1)
RY[b]	10	E_1 (1), E_2 (6), E_3 (3)
Redo operation ($n = 14$)		
RY on previous PT	5	E_1 (1), E_2 (3), E_4 (1)
RY on previous RY	9	E_2 (2), E_3 (2), E_4 (5)
Total	25	E_1 (3), E_2 (11), E_3 (5), E_4 (6)

[a] PT, primary repair over T-tube
[b] RY, Roux-en-Y hepaticojejunostomy

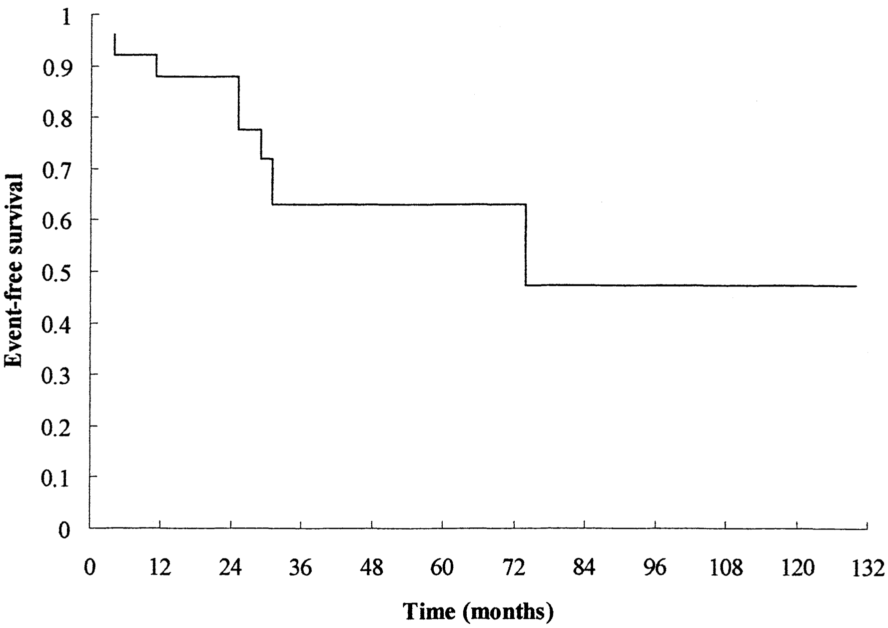


Fig. 3. Event-free survival in 25 patients with major bile duct injury after reconstructive surgery.

Table 3. Factors predictive of long-term outcomes after surgical repair for major bile duct injury at Cathay General Hospital (1990–1998)

	Total no. of patients $n = 25$	Success $n = 17$	Nonsuccess $n = 8$	p
Age (years)	54.4 ± 15.8	55.0 ± 16.5	53.3 ± 15.2	0.80
Gender				
Male	13 (5.8)[b]	10 (3.7)	3 (2.1)	0.29
Female	12 (6.6)	7 (3.4)	5 (3.2)	0.29
Operating time (min)	222.4 ± 56.9	215.4 ± 56.7	232.9 ± 57.1	0.53
Redo operation	14 (0.14)	11 (0.11)	3 (0.3)	0.20
Timing of surgery >2 months	15 (2.13)	10 (0.10)	5 (2.3)	0.61
Direct repair over T-tube as previous surgery	5 (0.5)	5 (0.5)	0 (0.5)	0.23
High level of injury (E_3, E_4)	11 (3.8)	6 (1.5)	5 (2.3)	0.20
Repair by nonreferral surgeon	5 (5.0)	1 (1.0)	4 (4.0)	0.02[a]
Perioperative inflammation	8 (4.4)	3 (1.2)	5 (3.2)	0.04[a]
Prolonged biliary-cutaneous fistula or PTC	5 (3.2)	3 (2.1)	2 (1.1)	0.53
Use of stent	8 (2.6)	5 (1.4)	3 (1.2)	0.51
Preoperative serum A1k $p > 400$ IU	14 (3.11)	10 (2.8)	4 (1.3)	0.50

[a] $p < 0.05$
[b] Further subdivisions of patients with positive risk factor are shown in the parentheses; the first figure represents the patient numbers in the primary repair group, and the second figure represents the patient numbers in the redo group

were redo surgeries, and we followed the patients longer. Among clinical factors predicting the long-term outcome, only two factors were statistically significant: repair performed by the same, i.e., nonreferral surgeon who performed the LC with complication of MBDI; and the presence of perioperative active inflammation in the same admission when the repair was performed. The reasons that repairs performed by the same LC surgeons proved to be a significant risk factor for nonsuccess lies in the fact that when a surgeon recognized a MBDI

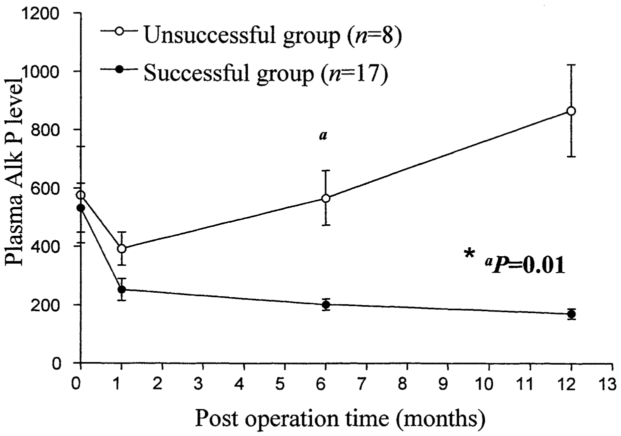
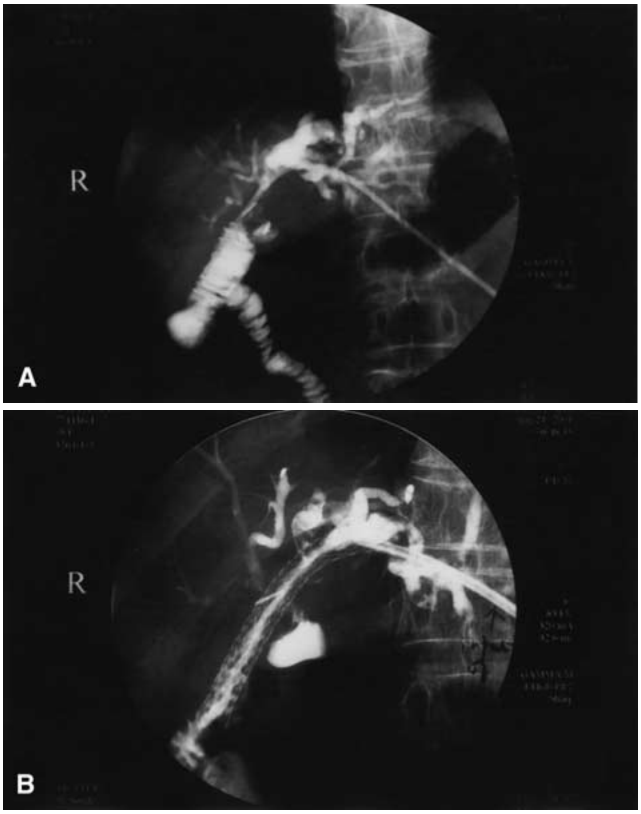


Fig. 4. Postoperative serum Alk P level of 25 patients receiving reconstructive surgery for major bile duct injury.

during LC, he usually converted the operation to open and repaired the MBDI himself. However, primary repair at this occasion is not easy because of the small size as well as the unclear margin of the viable duct. In addition, the experience of this LC surgeon who happened to confront such an unexpected MBDI may be insufficient to manage the MBDI in which a meticulous dissection of the liver hilum to prepare an adequate length of healthy proximal duct and a tension-free mucosa-to-mucosa anastomosis are necessary. Removal of all surgical clips on the duct stump and use of the proper suture materials are also important steps for a good repair. Our results showing a nonreferral surgeon as a risk factor are consistent with previous work by Soper et al. [12] and Strasberg et al. [13], who have suggested patients with biliary complications of LC should be referred to specialty centers for optimal care. Furthermore, our data show that concomitant recent active inflammation in the peritoneal cavity or biliary duct system, although it had been well controlled in the same admission before repair, was another significant predictor for long-term nonsuccess. This finding is consistent with that of Schol's report [11]. Tissue inflammation predisposes an area to scar formation. In this way, repair of a duct with recent inflammation or repair during a stage with coexisting active intraabdominal infection may predispose the anastomotic site to postoperative stricture. Percutaneous drainage is useful for an intraabdominal abscess or subhepatic bile collection. Diverting bile flow from the subhepatic space around an injury into a suprahepatic PTCD is a useful step to control active inflammation around injured ducts. However, remarkable inflammation and fibrosis of the proximal bile ducts were frequently observed in patients who had received biliary decompression with external drainage tubes (PTCD or subhepatic drainage) remaining for more than 2 months. The repair of ducts with active inflammation and fibrosis is very difficult. Dunkin et al. [4] demonstrated that the use of stents is associated with chronic inflammatory change of bile ducts in animal models. Although our data failed to demonstrate that preoperative drainage longer than 2 months or that the use of transanastomotic stents was associated with long-term nonsuccess, we are still in favor of using preoperative PTCD to release bile stasis and control infection around injured ducts, while using transanastomotic stenting for extremely difficult anastomoses in Strasburg class E_4 patients. However, because the drainage or stent tubes may have contradicted effects on the ducts for repair, we suggest not keeping the drainage tube or stent in place for too long. The redo operation for biliary stricture is technically difficult because of scar formation, anatomical change, and the lack of a healthy proximal duct for bilio-enteric anastomosis. Repair is difficult and time-consuming. Thus redo operations which most often also had high strictures (Strasberg classes E_3 and E_4) were considered significant risk factors for nonsuccess [6]. However, our data show no statistical differences in long term results between the primary and redo groups, which may be due to the small sample size of this study. Another explanation for this is that all the redo operations were performed by experienced referral surgeons, whereas only six of the 11 primary repairs were performed by experienced referral surgeons; the surgeon's experiences were quite different in these two groups. The surgical technique of experienced hands may overcome the difficulty of redo operations and get a better long-term results even when the MBDI is a high one. In eight of 14 patients who received redo operations, the confluences of the CHD were involved (E_3) or destroyed (E_4) either from previous surgery or by excision of the scar during the redo operation. In Strasberg class E_4 patients, the Hepp-Couinaud approach reported by Murr et al. [6] was only useful in reconstructing the left hepatic ducts. Enterobiliary anastomosis for completely separated right and left hepatic ducts remains a surgical challenge. Primary direct repair over a T-tube (PT) is a technique used by most surgeons to repair low CBD transections (Strasberg E_1) without extensive ductal tissue loss [11]. In general, a high success rate can be expected in the repair of this low injury. However, Roy et al. [10] reported that immediate PT repair was associated with a high failure rate. In this study, the five patients in the redo group had a PT as their unsuccessful previous repair, and the only patient on whom we used a PT as the primary repair also developed biliary stricture in postoperative long-term follow-up. All these experiences suggest that biliary-enteric anastomosis may be a better choice than PT repair as the primary procedure for all types of MBDIs.

We have demonstrated that a serum Alk P level higher than 400 IU in the sixth postoperative month is highly correlated with long-term non-success (Fig. 4). This implies that we may avert further redo operations by treating this subgroup of patients earlier, using therapeutic endoscopy or interventional radiology techniques as early as the sixth postoperative month even though the patients have no clinical symptoms but have image-proven stenosis.

In conclusion, this 2- to 10-year follow-up of 25 patients who received reconstructive surgery for LC-associated MBDI revealed that only 68% of patients had long-term success, which was less favorable compared to the immediate postoperative results. These guarded long-



Appendix 2. A, B Example of radiology-guided dilataion and stenting.

term results strongly support the importance of preventing bile duct injuries during LC. A high index of suspicion should be undertaken in patients who have undergone LC and are not recovering as quickly as expected, in order to diagnose and manage the MBDI as early as possible. Regardless of whether the injuries are recognized intraoperatively or later in the postoperative period, immediate referral to an experienced biliary specialist for further management is the best clinical decision for long-term success. For the referred patients, when clinical manifestations and the results of imaging studies indicate a surgical repair instead of nonsurgical management, one should avoid repair upon ducts with active inflammation or at a stage when there is coexisting or recent intraabdominal infection. A regular follow-up of postoperative serum Alk P levels for all patients with MBDI is strongly recommended. A serum Alk P level in the sixth postoperative month of greater than 400 IU suggests that anastomotic cicatrization is ongoing, and long-term stricture can be anticipated. In this case, early aggressive nonsurgical intervention, such as dilatation and stenting, may avert a subsequent reoperation.

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