



Size of recurrent symptomatic common bile duct stones and factors related to recurrence

BILIARY

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ABSTRACT

Background/Aims: Some common bile duct (CBD) stones recur after endoscopic stone extraction. Little information is available on the size and recurrence interval of recurrent symptomatic CBD stones or on ways to prevent recurrence.

Materials and Methods: Between January 2007 and December 2011, consecutive 481 patients undergoing endoscopic extraction of CBD stones at a single institute were enrolled. We selected 34 patients with recurrent symptomatic CBD stones and 63 patients who were followed up more than five years without recurrence.

Results: The sizes of the CBD stones increased during the recurrences: 10.1 ± 5.2 mm, 13.5 ± 7.3 mm, and 16.8 ± 7.8 mm at the initial presentation, the first recurrence, and the second recurrence, respectively ($p=0.016$). Among CBD stone recurrences, 50% occurred within 2.3 years, and 80% occurred within 5.3 years. The recurrence group had a smaller proportion of patients under 50 years of age, larger CBD diameters, less histories of more than 10 mm endoscopic papillary large-balloon dilation (EPLBD), and more type I periampullary diverticula, compared with the non-recurrence group ($p<0.05$). Multivariate analysis revealed that EPLBD more than 10 mm and smaller CBD diameter were independently related to less recurrence of CBD stones ($p=0.001$ and 0.012 , respectively).

Conclusion: The sizes of CBD stones increased during recurrences. EPLBD more than 10 mm and smaller CBD diameter were related to less recurrence of CBD stones.

Keywords: Cholelithiasis, gallstones, common bile duct, endoscopic retrograde cholangiopancreatography, recurrence

INTRODUCTION

Common bile duct (CBD) stones can be treated successfully by endoscopic stone extraction. Unfortunately, 4% to 24% of patients have recurrent CBD stones after the initial extraction of CBD stones (1-4). Some patients even have multiple recurrences. Unfortunately, little information is available on the characteristics of recurrent CBD stones or on the intervals of their recurrence, including multiple recurrences.

Common bile duct stone recurrence is an important issue because young patients have many years of future exposure, and elderly patients with frail or immunosuppressed conditions may have serious or life threatening events (5). For patients with significant risks of stone

recurrence, close follow-up, early intervention, and possible preventive measures should be performed (5).

Endoscopic sphincterotomy and stone extraction are well-established therapeutic procedures for the treatment of CBD stones. In addition to endoscopic sphincterotomy, endoscopic papillary balloon dilation (EPBD) is widely performed during endoscopic stone extraction. Since Ersoz et al. (6) introduced endoscopic papillary large-balloon dilation (EPLBD) of more than 12 mm in 2003, it has been recommended for large CBD stone removal. However, for the recurrence of CBD stones, the role of EPLBD has not been established. Recently, it has been reported that more than 15 mm EPLBD prevented the short-term recurrence of CBD stones (7)

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while EPLBD (12 mm to 20 mm) reduced recurrence in patients with periampullary diverticula (8). Because large balloon dilation carries the risk of complications when the CBD is not adequately dilated or has a stricture, EPLBD should be performed cautiously, according to the CBD diameter. In patients with CBD diameter less than 12 mm, 10 mm EPBD may be sufficient for stone extraction. However, the benefit of EPLBD, including 10 mm dilations, for prevention of recurrence has not been studied.

Therefore, we evaluated the role of EPLBD (≥ 10 mm) in preventing the recurrence of CBD stones while identifying risk factors related to recurrence. Furthermore, the characteristics of symptomatic recurrent CBD stones and the interval of recurrence were investigated in patients with the first, second, and third recurrences of CBD stones.

MATERIALS AND METHODS

Patients

Between January 2007 and December 2011, 481 patients undergoing endoscopic extraction of CBD stones at a single institute were enrolled consecutively. Endoscopic retrograde cholangiopancreatography (ERCP) was performed when the imaging study and laboratory tests indicated CBD stones with or without cholangitis. The CBD stones found six months or more after an endoscopic extraction were defined as recurrent CBD stones to exclude retained CBD stones (9-11). Patients who had recurrent CBD stones more than once were enrolled in the recurrence group and analyzed retrospectively (Figure 1). For the non-recurrence group, we selected patients who had undergone endoscopic stone extraction in 2007 and then followed up more than five years without recurrence in order to exclude potential patients with future recurrence of CBD stone during follow-up as much as possible. We performed EUS in the non-recurrence group in five years to confirm no stone in

CBD. Patients with certain conditions were excluded, as follows: biliary stricture, liver cirrhosis, hepatocellular carcinoma, pancreas cancer, bile duct cancer, stone in gallbladder during follow-up, and major surgery involving pancreatobiliary system. Patient anonymity was preserved, and the Institutional Review Board of our hospital approved this study. The study protocol was in complete compliance with the Declaration of Helsinki, as revised in Seoul in 2008.

Endoscopic extraction of common bile duct stones

Endoscopic retrograde cholangiopancreatography was performed using a duodenoscope (JF 240; Olympus Optical Co., Ltd., Tokyo, Japan). All patients underwent endoscopic sphincterotomy before the stone extraction. In cases with large CBD stone, bleeding tendency, or periampullary diverticulum, papillary balloon dilation was considered. Papillary balloon dilation (10 mm to 20 mm) was achieved using a controlled radial expansion balloon dilator (CRE™; maximum diameter 12 mm, 15 mm, 18mm, or 20 mm, Boston Scientific Co., Natick, MA, USA) or a Hurricane RX dilation balloon (maximum diameter 10 mm, Boston Scientific Co., Natick, MA, USA). Before balloon dilation, small sized endoscopic sphincterotomy was performed. The bile duct was swept with a basket and a retrieval balloon catheter to remove the calculi. If a stone basket was trapped in the CBD, mechanical lithotripsy was performed. In all patients who had undergone endoscopic extraction of CBD stones, an endoscopic nasobiliary drainage (ENBD) tube was inserted. Tubography via the ENBD tube was performed to confirm the absence of residual stones in the CBD one or two days later.

Assessment of risk factors for CBD stone recurrence

Periampullary diverticula were classified as type I, II, or III according to the position of the major papilla from the endoscopic view (12). In type I, the major papilla was located inside of the diverticulum; in type II, the major papilla was located in the margin of the diverticulum; and in type III, the major papilla was located outside of the diverticulum. To measure the CBD diameters, CBD angle, and sizes of the CBD stones, CT, MRCP, or cholangiography data sets were transferred to picture archiving and communication system (PACS) workstations. The diameters were measured using electronic calipers on the PACS workstation. The largest diameter perpendicular to the long axis of the CBD was selected as a representative CBD diameter. Angulation of CBD was measured as the sharpest angle along the CBD from 1 cm below the bifurcation to 1 cm above the papilla (9,13). The longest diameter of the largest CBD stone was selected as a CBD stone diameter.

Statistical analysis

In the comparisons among the initial, first, and second recurrence patients, one-way analysis of variance (ANOVA) or Pearson's chi-square tests were used. Mann-Whitney U tests or paired t tests were applied for subgroup analysis. Cumulative recurrence rate curves were plotted and compared by the Kaplan-Meier method and log rank test. Specific cumulative

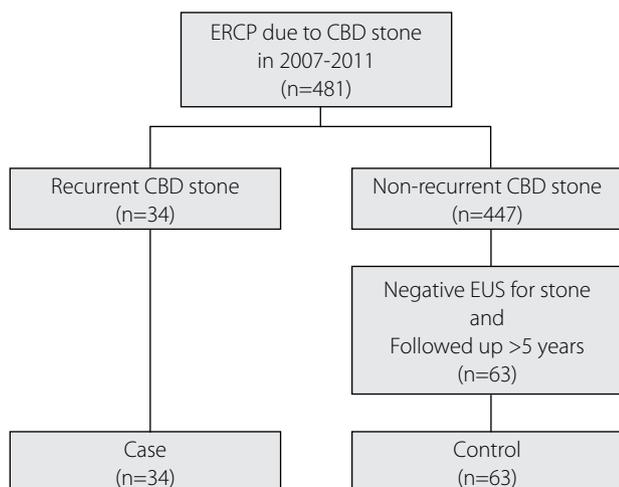


Figure 1. Study population.

Table 1. Characteristics of the initial, first, and second recurrent common bile duct stones

Characteristics	CBD stones			p value
	Initial	1 st recurrence	2 nd recurrence	
No. of patients	34	34	12	
Age, mean±SD (yr)	65.2±12.5	65.2±12.5	72.2±10.6	0.176
Male sex	14 (41%)	14 (41%)	4 (33%)	0.739
Recurrence interval, mean±SD (days)		1409±1157	1291±1013	0.653
No. of stones, mean±SD	2.2±2.1	2.2±1.4	2.2±1.7	1.000
Size of the largest stone, mean±SD (mm)*	10.1±5.2	13.5±7.3	16.8±7.8	0.016
CBD diameter, mean±SD (mm)	16.5±5.3	16.1±6.0	17.7±4.7	0.676
CBD angle, mean±SD (°)	128±15	124±18	133±15	0.265

SD: standard deviation; CBD: common bile duct; SD: standard deviation

*Initial vs. 1st recurrence, $p=0.006$.

rates were estimated in a life-table. Pearson's chi-square tests or Student's t tests were used to compare the recurrence group and the non-recurrence group. Multivariate analyses were performed with logistic regression analysis to determine the factors related to the recurrence of CBD stones. All statistical analyses were performed with SPSS, version 20 (SPSS, Inc., Chicago, IL, USA). P values <0.05 were considered significant.

RESULTS

Patient characteristics

A total of 97 patients consisting of 34 patients with recurrent CBD stones and 63 patients without recurrence were selected. The mean age of the patients was 62.9 ± 15.7 years, and males comprised 43% of the population. The recurrence times ranged from a minimum of one to a maximum of four in the same patient. Thirty-one (32%) patients did not undergo cholecystectomy after ERCP, but none of them had gallbladder stones.

Size and recurrence interval of recurrent common bile duct stones

Among the 34 patients with recurring CBD stones, 12 had a second recurrence, four had a third recurrence, and one had a fourth recurrence. The characteristics and related clinical information pertaining to the initial, first, and second recurrent CBD stones are shown in Table 1. All recurrent stones were brown pigment stones. The recurrence interval between the initial presentation and the first recurrence was similar to that between the first and second recurrence: 1409 ± 1157 days and 1291 ± 1013 days, respectively ($p=0.653$). The size of the largest stone was significantly increased during recurrences: 10.1 ± 5.2 mm at the initial presentation, 13.5 ± 7.3 mm at the first recurrence, and 16.3 ± 7.8 mm at the second recurrence ($p=0.016$). The number of stones, CBD diameter, and CBD angle did not differ according to the recurrences. In the analysis of the recurrent intervals of the CBD stones, 50% of the first and overall recurrences of CBD stones occurred within 27.8

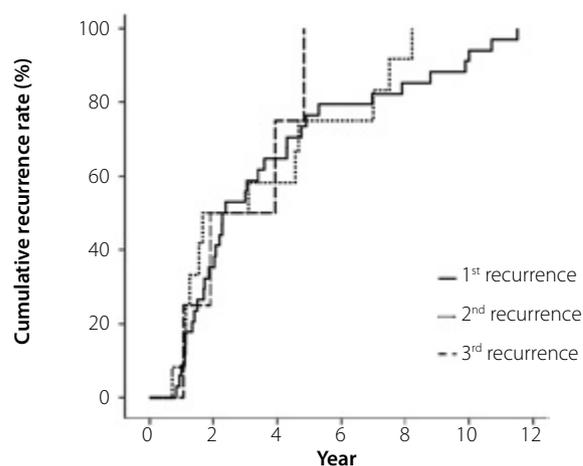


Figure 2. Cumulative recurrence rates of the first, second, and third recurrences of the CBD stones according to recurrence intervals. The cumulative rates did not differ among the three groups (log rank test, $p\geq 0.531$).

months, and 80% occurred within 5.3 years (range 10 to 140 months). The cumulative recurrence rates, according to the recurrence interval, did not differ among the first, second, or third recurrence groups (Figure 2), ($p\geq 0.531$). The recurrence rates slowed after five years in the overall cumulative recurrence rate curve.

Comparison between the recurrence group and the non-recurrence group

The recurrence group had a smaller proportion of patients under 50 years of age, larger CBD diameters, less histories of more than 10 mm EPLBD, and more type I periampullary diverticula, compared with the non-recurrence group ($p=0.038$, 0.001, 0.014, and 0.030, respectively) (Table 2). Although it was not statistically significant, the number of patients with intrahepatic stones was larger in the recurrence group (6, 18%) than in the non-recurrence group (4, 6%). The size and number of stones did not differ between the two groups. Among patients with CBD diameters less than 12 mm, no recurrence

Table 2. Comparison between the recurrence group and the non-recurrence group

	CBD stone		p value
	Recurrence	Non-recurrence	
No. of patients	34	63	
Age, mean±SD (yr)	65.2±12.5	61.6±17.2	0.249
≥80	3 (9%)	7 (11%)	1.000
<50	3 (9%)	17 (27%)	0.038
Male sex	14 (41%)	28 (44%)	0.757
Gallbladder			
Intact*	9 (26%)	22 (35%)	0.394
Cholecystectomy state	25 (74%)	41 (65%)	0.394
Classification of primary stones			0.782
Brown pigment	22	45	
Mixed	7	10	
Black pigment	5	8	
Patients with intrahepatic stones	6 (18%) [†]	4 (6%)	0.094
No. of CBD stones, mean±SD	2.2±2.1	2.3±1.6	0.808
Size of the largest initial CBD stone, mean±SD (mm)	10.1±5.2	10.6±7.6	0.877
CBD diameter, mean±SD (mm)	16.5±5.3	12.2±6.1	0.001
CBD angle, mean±SD (°)	128±15	129±14	0.582
Endoscopic sphincterotomy (ES) or endoscopic papillary large-balloon dilation (EPLBD)			
ES	34 (100%)	63 (100%)	1.000
ES + EPLBD (≥10 mm)	10 (29%)	35 (56%)	0.014
Size of balloon dilation, mean±SD (mm)	12.3±2.0	12.7±2.5	0.563
Mechanical lithotripsy	2 (6%)	3 (5%)	1.000
Periampullary diverticulum	15 (44%)	23 (37%)	0.464
Type I	7	3	0.030
Type II	2	11	0.131
Type III	6	9	0.662

CBD: common bile duct; SD: standard deviation

*All patient had no gallstone; [†]Three patients underwent removal of intrahepatic stones by operation.

was seen in patients with EPLBD more than 10 mm. Among patients with CBD diameters more than 12 mm, patients with EPLBD more than 10 mm showed significantly lower recurrence rate than those without EPLBD ($p=0.036$). Multivariate analysis was performed using four factors that were significant in univariate analysis (Table 3). EPLBD more than 10 mm and CBD diameter were independent factors related to the recurrence of CBD stones (OR 0.161, $p=0.001$ and OR 1.126, $p=0.012$, respectively).

Table 3. Multivariate analysis of the factors related to the recurrence of common bile duct stones

Factors	OR (95% CI)	p value
Endoscopic papillary large-balloon dilation (≥10 mm)	0.161 (0.055-0.473)	0.001
CBD diameter	1.126 (1.027-1.235)	0.012
Type I periampullary diverticulum	3.322 (0.608-18.17)	0.166
Age (<50)	0.314 (0.073-1.360)	0.122

OR: odds ratio; CI: confidence interval; CBD: common bile duct

DISCUSSION

The present study demonstrated that the size of CBD stones increased during recurrences, and that EPLBD more than 10 mm and smaller CBD diameter were related to less recurrence of CBD stones. Half of the recurrences occurred within 2.3 years, and 80% occurred within 5.3 years.

The studies concerning the recurrence interval and frequency of CBD stones after endoscopic stone extraction are insufficient. In addition, those with multiple recurrences had not previously been studied. The reported mean or median intervals until the first recurrence were given as 13-33 months (10,14,15). One study showed that 70% of the stones recurred within five years (14). In the present study, 50% of the first recurrences of CBD stones occurred within 2.3 years, and 80%, within 5.3 years. Therefore, the follow-up could be determined in consideration of the recurrence interval. Careful follow-up should be performed until at least five years after the endoscopic stone extraction because 80% of patients experienced recurrences within approximately five years, and the recurrence rates slowed after five years. Our study demonstrated that there were no differences in the recurrence intervals among the first, second, and third recurrences. This results indicates that the follow-up interval for the first recurrence could be applied for the second or third recurrence.

The characteristics of recurrent stones are remained uncertain, and the comparison among multiple recurrent stones has not been studied before. In one study, all of the recurrent stones were bilirubinate, irrespective of the type of stone at the initial incidence (14). The fact that the recurrent stones are invariably of the bilirubinate type, irrespective of the type of stones at the initial presentation, suggests that bacterial infestation due to ablation of the sphincter mechanism may play a causative role (14). In the present study, the recurrent stones were all brown pigment stones. Our study demonstrated that the symptomatic recurrent stones became larger as successive recurrences. However, the recurrence interval, stone number, CBD diameter, and CBD angle did not differ among the initial, first, and second recurrences. Interestingly, the second and third recurrent stones were also larger than the previous stone in the present study. Greater incidence of ascending infection and lower CBD stone density may be possible explanations, but this needs to be studied further.

Risk factors related to the recurrence of CBD stones have been widely studied. The possible risk factors include CBD diameter, periampullary diverticulum, curved CBD angle, old age, multiple sessions of ERCP, multiple CBD stones, gallbladder left in situ, lithotripsy, pneumobilia, etc. (4,5,9-11,16-18). The present study demonstrated that CBD diameter and EPLBD more than 10 mm were independent factors related to recurrence upon multivariate analysis. EPLBD is a new method that employs a large-diameter balloon catheter to remove CBD stones that cannot be extracted by conventional techniques (7). Despite the advantages of EPLBD, there are some concerns for adverse events during EPLBD. The reported overall rate of adverse events is 5% (0%-14%) (19). The most frequent adverse events were pancreatitis and bleeding, occurring in 2.8% (0%-8%) and 1.2% (0%-6.7%) of patients, respectively (19). No cases of severe pancreatitis were reported, nor did we encounter severe pancreatitis or bleeding in the study. Although EPLBD has the benefits of facilitating the extraction of stones and preventing recurrences, EPLBD should be avoided in patients with insufficiently dilated CBD or biliary stricture. Forced balloon dilation greater than CBD diameter can lead to complications such as perforations (20). From our study, EPLBD with balloon of the proper size that is more than 10 mm, according to the CBD diameter, can prevent complications and recurrences of CBD stones.

The follow-up periods of previous studies varied and included many patients receiving short follow-ups. Several patients in the non-recurrence group in previous studies could have recurrences over further follow-up. Our study selected a control group who had already been followed for more than five years. Therefore, there was less of a possibility of recurrence due to the short follow-up period in the non-recurrence group. These precautions may constitute a merit of our study.

There were some limitations to the present study. First, this was a retrospective case control study and the number of patient with recurrence was relatively small. However, we found some statistical significance in different groups. Prospective studies with large number of patients would make the comparison efficient. Second, analysis of separate groups with primary or secondary CBD stones would be more informative. Because the proportions of classification of CBD stones in our study did not differ in the recurrence and the non-recurrence group, we suppose that the proportion of primary and secondary stones also did not differ between two groups. Moreover, all recurrent stones were brown pigment stones and there was no stone in gallbladder in all following patients without cholecystectomy. Hence, there are few possibilities of secondary CBD stones in the recurrence group.

In conclusion, the size of CBD stones increased during recurrences. EPLBD more than 10 mm and smaller CBD diameter were related to less recurrence of CBD stones. We expect that

a prospective large-scale study with long follow-ups on recurrent CBD stones will be performed in the near future.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

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