PANCREAS AND BILIARY

Endoscopic retreatment of recurrent choledocholithiasis after sphincterotomy

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Background: Endoscopic sphincterotomy (ES) carries a substantial risk of recurrent choledocholithiasis but retreatment with endoscopic retrograde cholangiopancreatography (ERCP) is safe and feasible. However, long term results of repeat ERCP and risk factors for late complications are largely unknown.
Aims: To investigate the long term outcome of repeat ERCP for recurrent bile duct stones after ES and to identify risk factors predicting late choledochal complications.
Methods: Eighty four patients underwent repeat ERCP, combined with ES in 69, for post-ES recurrent choledocholithiasis. Long term outcomes of repeat ERCP were retrospectively investigated and factors predicting late complications were assessed by multivariate analysis.
Results: Complete stone clearance was achieved in all patients. Forty nine patients had no visible evidence of prior sphincterotomy. Two patients experienced early complications. During a follow up period of 2.2–26.0 years (median 10.9 years), 31 patients (37%) developed late complications, including stone recurrence (n = 26), acute acalculous cholangitis(n = 4), and acute cholecystitis (n = 1). There were neither biliary malignancies nor deaths attributable to biliary disease. Multivariate analysis identified three independent risk factors for choledochal complications: interval between initial ES and repeat ERCP $\leqslant$5 years, bile duct diameter $\geqslant$15 mm, and periampullary diverticulum. Choledochal complications were successfully treated with repeat ERCP in 29 patients.
Conclusions: Choledochal complications after repeat ERCP are relatively frequent but are endoscopically manageable. Careful follow up is necessary, particularly for patients with a dilated bile duct, periampullary diverticulum, or early recurrence. Repeat ERCP is a reasonable treatment even for recurrent choledocholithiasis after ES.

Endoscopic sphincterotomy (ES) has been widely accepted as an effective and minimally invasive treatment for choledocholithiasis. ES carries a substantial risk of long term choledochal complications, including recurrent stones and acute cholangitis. Although the complication rate is not negligible (5.8–24% for a mean follow up period exceeding 10 years),[1–6] retreatment with endoscopic retrograde cholangiopancreatography (ERCP), whether combined with repeat ES or not, has been reported to be safe and feasible.[1–3 6–9] However, little information is available on the long term outcome of repeat ERCP. Furthermore, risk factors for re-recurrence after repeat ERCP have not been studied. Herein we investigated the long term (median 10.9 years) results of repeat ERCP for recurrent bile duct stones after ES and identified risk factors predicting late choledochal complications by multivariate logistic regression analysis.

PATIENTS AND METHODS

Between 1977 and 1998, 84 patients underwent repeat therapeutic ERCP for post-ES recurrent choledocholithiasis. There were 40 men and 44 women with a mean age of 71 (range 31–91) years. Patients with concomitant hepatolithiasis, choledochal cyst, or bile duct stricture were excluded from the present study. These patients had undergone initial ES with complete clearance of bile duct stones 0.9–17.2 years (median 4.4) earlier. During the same time period, 783 patients underwent initial ES for choledocholithiasis at our hospital. ES was performed using a standard "pull" technique, with the maximum extent of the cut being the junction between the roof of the papillary fold and the duodenal wall (medium or large sphincterotomy). Of the present 84 patients, the initial ES had been performed at our hospital in 53 and at other hospitals in 31.

Early and long term outcomes were retrospectively investigated in these 84 patients. Early (<30 days) complications were defined and graded according to the criteria of Cotton and colleagues.[10] Long term (>5 years) follow up data were obtained from our outpatient records or from the patients, their families, and/or their local practitioners by mail and/or telephone, in December 2003. Data included: (1) biliary symptoms (abdominal pain, jaundice, fever, and chills); (2) medical investigations (liver function tests and imaging studies), if performed; (3) medical and surgical treatment; and (4) cause of death since the initial ES. If symptoms, liver function tests, abdominal ultrasonography, and/or magnetic resonance cholangiopancreatography indicated possible biliary pathology, patients were advised to undergo repeat diagnostic ERCP.

Late complications were classified as choledochal complications (acute cholangitis and bile duct stone recurrence) and acute cholecystitis. The cumulative rate of late choledochal complications occurring during follow up was determined using the Kaplan-Meier method. To identify risk factors predictive of late choledochal complications after repeat ERCP, patient or ERCP related factors were analysed. The 15 potential risk factors listed in table 2 were assessed by univariate analysis using the χ^2 test. Predictors with a p value <0.1 in the univariate analysis were then included in a forward stepwise multiple logistic regression model using the SPSS 11.0 statistical system for Windows. Differences were considered significant when $p<0.05$.

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy

Table 1 Late complications after repeat ERCP in 84 patients with recurrent choledocholithiasis

Complications	No
Choledochal complications	30 (36%)
Bile duct stone recurrence	26
With no visible evidence of prior sphincterotomy	15
With enlarged biliary orifice	11
Cholangitis without stone recurrence	4
With no visible evidence of prior sphincterotomy	4
Acute cholecystitis	1 (1%)
Total	31 (37%)

RESULTS

All 84 patients successfully underwent transpapillary stone extraction with a basket or balloon catheter, or a mechanical lithotriptor, combined with repeat ES in 69 patients. Bile duct clearance was achieved after one endoscopic procedure in 74 and after 2–3 procedures in 10 patients. At recurrence, all patients had brown pigment stones. On ERCP, the biliary orifice (sphincterotomy site) was found to be enlarged in 35 patients (42%) and not enlarged (mild deformity of the papilla but no visible evidence of prior sphincterotomy) in 49 (58%). None showed papillary stricture preventing cannulation. Forty eight patients with enlarged biliary orifice (n = 19) or with no visible evidence of prior sphincterotomy (n = 29) presented with acute cholangitis but none had acute gall stone pancreatitis before repeat ERCP. After repeat ERCP, early complications developed in two patients (2%), including mild haemorrhage in one and mild acute pancreatitis in the other. There were no ERCP related deaths.

Of the 84 patients, 62 had previously undergone cholecystectomy, combined with bile duct exploration in 50. In the 22 remaining patients with (n = 11) or without (n = 11) cholelithiasis, the gall bladder was left in situ after repeat ERCP.

All 84 patients were followed up until termination of the study (December 2003) or death. The overall duration of follow up ranged from 2.2 to 26.0 years (median 10.9; mean 11.7). During the follow up period, 19 patients had died at 2.2–24.4 years (median 8.3; ⩽5 years in five patients, >5 years in 14) after repeat ERCP. All died from non-biliary diseases.

Of the 84 patients, 31 (37%) experienced biliary symptoms during follow up (table 1). These symptoms were attributed to bile duct stone recurrence (n = 26), acute cholangitis without recurrent stones probably due to no visible evidence of prior sphincterotomy (not stricture) (n = 4), or acute cholecystitis (n = 1) (table 1). After repeat ERCP, neither liver abscess nor biliary malignancy developed in any of our cases.

Choledochal complications (n = 30, 36%) occurred 1.1–11.1 years (median 3.4 years) after repeat ERCP. The cumulative incidence of choledochal complications was 28% at 5 years, 37% at 10 years, and 39% at 15 and 20 years (fig 1). Most complications occurred during the first five years.

Of 26 patients with re-recurrent choledocholithiasis, 25 successfully underwent transpapillary stone extraction, combined with repeat ES in 21. The remaining patient underwent choledochojejunostomy without further recurrence for 4.5 years. Of these 26 patients, all had brown pigment stones and 15 (58%) were not found to have an enlarged biliary orifice at re-recurrence. None showed papillary stricture. Four patients with acute cholangitis, but no bile duct stone recurrence, underwent repeat ES because of no visible evidence of prior sphincterotomy. Of 29 patients receiving a third ERCP, none experienced early complications. Three of the 29 patients developed a third recurrence of bile duct stones 1.7–3.3 years (median 3.0) later. Two patients underwent repeat ES and the other choledochojejunostomy without further recurrence for 2.7–6.1 years.

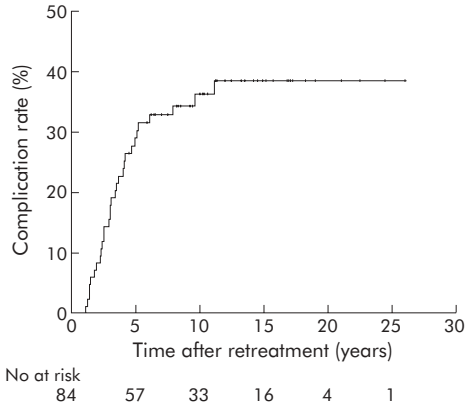

Figure 1 Kaplan-Meier plot for the cumulative rate of late choledochal complications in 84 patients who underwent repeat endoscopic retrograde cholangiopancreatography for recurrent choledocholithiasis.

Among the 15 potential risk factors for choledochal complications, the following four were significant according to univariate analysis: interval between initial ES and repeat ERCP ⩽5 years, bile duct diameter ⩾15 mm, stone diameter ⩾15 mm, and periampullary diverticulum (table 2). Multivariate analysis identified three independent risk factors: interval between initial ES and repeat ERCP ⩽5 years, bile duct diameter ⩾15 mm, and periampullary diverticulum (table 3).

Of 22 patients with gall bladder in situ, one (5%) with cholelithiasis developed acute cholecystitis 2.1 years after repeat ERCP, which necessitated cholecystectomy. The incidence of cholecystitis was 9% (one of 11) for patients with gall bladder stones and 0% (none of 11) for those with an acalculous gall bladder. No other patients experienced symptoms attributable to gall bladder stones.

Of the 84 patients, 53 (63%) were free of biliary symptoms as of December 2003 or until death. During follow up, 11 of 53 patients underwent repeat diagnostic ERCP, mostly because of mild cholestatic liver dysfunction or suspected bile duct stones on imaging study; five of the 11 patients underwent ERCP between 2000 and 2003. However, none of these patients had evidence of recurrent choledocholithiasis or papillary stricture on ERCP.

DISCUSSION

In the present study, endoscopic stone extraction combined with repeat ES (in 82% of patients) was successful in all patients with post-ES recurrent choledocholithiasis. The early complication rate was very low (2%). The anatomical landmark for guiding sphincterotomy length is sometimes obscure. However, repeat ES which is delayed rather than performed immediately after initial ES is reportedly safer than initial ES.[9]

The late choledochal complication rate after repeat ERCP was relatively high (36% during the median follow up period of 10.9 years). This is higher than the rates (5.8–24%)[1–6] reported after initial ES. The interval (3.4 years) between repeat ERCP and re-recurrence was shorter than that (4.4 years) between initial ES and repeat ERCP. Furthermore, a third recurrence occurred relatively frequently (10%) and early (3.0 years). Patients who have developed recurrent bile duct stones after initial ES seem to be at high risk of recurrence after repeat ERCP. Repeat ES does not seem

Table 2 Univariate analysis of potential risk factors for choledochal complications

Risk factor	All patients	Patients with complications	p Value
Age ⩽70 y (yes/no)	40/44	11/19	0.134
Sex (male/female)	37/47	13/17	0.922
Interval between initial ES and repeat ERCP ⩽5 y (yes/no)	43/41	20/10	0.034
Bile duct diameter ⩾15 mm (yes/no)	49/35	22/8	0.035
Bile duct stone diameter ⩾15 mm (yes/no)	38/46	18/12	0.043
Bile duct stone number ⩾5 (yes/no)	30/54	14/16	0.118
Previous cholecystectomy (yes/no)	62/22	22/8	0.941
Previous duct exploration (yes/no)	50/34	17/13	0.691
Gall bladder stones (yes/no)	11/11	5/3	0.375
Periampullary diverticulum (yes/no)	33/51	16/14	0.043
Previous or present cholangitis (yes/no)	48/36	17/13	0.948
Pneumobilia (yes/no)	59/25	20/10	0.594
No visible evidence of prior sphincterotomy (yes/no)	49/35	17/13	0.817
Re-sphincterotomy (yes/no)	69/15	24/6	0.702
Mechanical lithotripsy (yes/no)	50/34	22/8	0.051

ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy.

to prevent or reduce the likelihood of further stone formation.

In surgical series, late complication rates are reportedly 5–16% after primary bile duct exploration (mean follow up 4.8–10 years), 13.4–33% after duct re-exploration (5–16 years), and 0–32% after choledochoenterostomy (2.4–21.1 years).[7] Accordingly, the present results are comparable with those of surgical re-treatment. Furthermore, choledochal complications after repeat ERCP could be managed safely and effectively with re-repeat (three or more) ERCP. In patients with multiple recurrences, repeat ERCP is a reasonable treatment although surgical biliary drainage procedures (choledochoenterostomy or transduodenal sphincteroplasty) may be considered, particularly in younger and more healthy patients. Endoscopic balloon dilation has been reported to be useful for treating post-ES complications due to papillary stricture,[11] although none of the present cases underwent this procedure.

Although the causes of recurrence after initial ES for choledocholithiasis have not been fully clarified, several factors have been proposed, including pre-existing patient related factors (bile composition and biliary anatomy) and ES related factors (sphincter ablation and papillary stenosis).[6–9 11–18] Almost all recurrent stones are brown pigment stones, irrespective of stone classification at initial ES.[1 3 4 6] Biliary infection may play an important role in the pathogenesis of recurrent stones[19] because brown pigment stones are generally considered to result from bacterial infection.[20] In the present study, all recurrent and re-recurrent stones were brown pigment stones. A similar mechanism may be involved in re-recurrence. In many (58%) cases, re-recurrent stones were associated with no visible evidence of prior sphincterotomy (not stricture). However, patients with a wide open sphincterotomy can also develop re-recurrent stones, as in the case of initial recurrence[1 4 6] Therefore, the causes of re-recurrence seem to be multifactorial.

Previous studies have identified factors predictive of choledochal complications after initial ES: a dilated bile duct,[6–9 12–18] brown pigment stones at ES,[6] periampullary diverticula,[7 12] mechanical lithotripsy,[13] pneumobilia,[13] in situ gall bladder,[7] and small sphincterotomy.[18] The present multivariate analysis identified three independent risk factors predictive of choledochal complications after repeat ERCP: interval between initial ES and repeat ERCP ⩽5 years, bile duct diameter ⩾15 mm, and periampullary diverticulum. A dilated bile duct may contribute to choledochal complications via bile stagnation and bacteriobilia. Periampullary diverticula may cause bacterial overgrowth and motility disturbance[21 22] which could persist after ES. The underlying condition promoting early recurrence after initial ES apparently remains unchanged, even after repeat ERCP. During long term follow up, the sphincterotomy site usually shows natural shrinkage[23 24] and rarely stricture.[11] Papillary stenosis (true stricture and mild narrowing or no visible evidence of prior sphincterotomy) after ES seems to cause choledochal complications.[2 5 11 18] However, repeat ES can improve papillary stenosis. The present study which did not include cases of papillary stricture did not identify no visible evidence of prior sphincterotomy (at repeat ERCP after first recurrence) as a risk factor for re-recurrence.

In the present study, only 5% of patients with gall bladder in situ developed acute cholecystitis after repeat ERCP: 9% of those with gall bladder stones and none of those with an acalculous gall bladder. ES does not adversely affect gall bladder motility[24] and is unlikely to increase the risk of acute cholecystitis, particularly in acalculous gall bladder cases.[4 6 7 13]

In conclusion, repeat ERCP for post-ES recurrent choledocholithiasis is associated with a relatively high incidence of late choledochal complications (recurrent bile duct stones and acute cholangitis). Careful follow up after repeat ERCP is necessary, particularly for patients with a dilated bile duct,

Table 3 Multivariate analysis of potential risk factors for choledochal complications

Risk factor	Adjusted odds ratio	95% adjusted CI	p Value
Bile duct diameter ⩾15 mm	6.41	1.92–21.34	0.003
Interval between initial ES and repeat ERCP ⩽5 y	4.19	1.38–12.76	0.012
Periampullary diverticulum	3.16	1.07–9.31	0.037
Bile duct stone diameter ⩾15 mm			0.124
Mechanical lithotripsy			0.158

Factors with a p value <0.1 by univariate analysis (table 2) were included in the multivariate analysis.
CI, confidence interval.

periampullary diverticulum, or early recurrent choledocholithiasis, given the high incidence of choledochal complications. However, repeat (three or more) ERCP is safe and effective for managing choledochal complications. Repeat ERCP, with or without ES, is a reasonable treatment even for recurrent choledocholithiasis after ES.

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