BILIARY DISEASE

Risk factors for recurrent bile duct stones after endoscopic papillotomy

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Gut 2003;52:116-121

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Accepted for publication
12 June 2002

Background: The long term outcome of endoscopic papillotomy (EPT) is not well known. The aims of this study were to clarify the clinical course of post-EPT patients and to detect predictors for bile duct stone recurrence.

Methods: A total of 1042 consecutive patients who underwent EPT for bile duct stones from December 1975 to September 1998 were prospectively followed up. Patients were divided into four groups according to gall bladder (GB) status: "acalculous GB" group, "calculous GB" group, "cholecystectomy" group, and "prior cholecystectomy" group. Reliable follow up information was obtained for 983 (94.3%) of the 1042 patients. The following factors were considered in the evaluation of predisposing risk factors for recurrence of bile duct stones: age, sex, gall bladder status, periampullary diverticulum, number of bile duct stones, diameter of bile duct stones, diameter of bile duct, lithotripsy, precutting, pneumobilia, and early complications.

Results: Recurrence occurred in 111 patients. The "acalculous GB" group was less prone to recurrence than the "prior cholecystectomy" group and the "calculous GB" group. The relative risks (RR) for the latter two compared with the former group were 2.26 (95% confidence interval (CI) 1.24-4.14; $p=0.0078$) and 2.16 (95% CI 1.21-3.87; $p=0.0093$), respectively. Other prognostic factors were lithotripsy (RR 2.37; 95% CI 1.47-3.81; $p=0.0004$) and pneumobilia (RR 1.57; 95% CI 1.01-2.43; $p=0.044$).

Conclusions: Gall bladder status, lithotripsy, and pneumobilia were significantly related to bile duct stone recurrence after EPT.

Endoscopic papillotomy (EPT) was first introduced in 1974 as a treatment for choledocholithiasis.^{1,2} The safety of EPT has been well established and its use has become widespread. In the early stages, its indication was limited to remnant or recurrent bile duct stones after cholecystectomy. With the spread of EPT, its indication has been extended to patients who have an intact gall bladder without cholelithiasis, and recently patients who have an intact gall bladder with cholelithiasis are regarded as a relative indication. Nevertheless, the rate of recurrence of stones and predictors of bile duct stone recurrence are not well known. The aims of this study were to clarify the clinical course of post-EPT patients and to detect the predictors of stone recurrence.

METHODS

Patients

From December 1975 to September 1998, 1289 consecutive patients with choledocholithiasis were treated. The diagnosis of choledocholithiasis was made based on radiological visualisation (ultrasonography, computed tomography, cholangiography) of bile duct stones and/or the presence of cholestasis (high levels of γ glutamyl transferase, alkaline phosphatase, total bilirubin) associated with both bile duct dilatation (greater than 8 mm) and laceration of the major papilla (confirmed endoscopically). Of these patients, 138 were excluded for the following reasons: two were travellers from abroad; eight had concomitant pancreaticobiliary malignancy; and 128 had concomitant hepatolithiasis. EPT and bile duct stone removal were achieved in 1042 (91%) of the 1151 patients. These 1042 patients were included in this study.

Endoscopic treatment

A papillotome provided with a wire 10 mm in length was used in the pure cut setting. To avoid perforation and bleeding, the

papillotome was positioned so that the incision was made only in the distal portion of the intramural part of the common bile duct. The precut papillotomy technique was used in certain cases.

Before October 1978, patients were treated with EPT alone because endoscopic techniques for stone extraction had not yet been developed. In this period, spontaneous stone passage was confirmed by endoscopic retrograde cholangiography two weeks to one month after EPT. From November 1978 basket extraction was performed to remove small stones with a diameter of 10 mm or less. In February 1987, mechanical lithotripsy was introduced to fragment stones greater than 10 mm in diameter, and since October 1989 certain difficult cases have been treated with electrohydraulic lithotripsy or flash-lamp pumped dye laser using a "mother-baby" endoscope system.

For each procedure, patient data (age, sex, gall bladder status, findings on x ray films), treatment (need for lithotripsy, need for precutting), and clinical course were prospectively determined and recorded in our database system.

Definitions

Number of bile duct stones, diameter of bile duct stones, and diameter of the bile duct were determined by endoscopic retrograde cholangiography. The presence/absence of periampullary diverticulum was determined at the same time.

Before July 1979, the presence/absence of gall bladder stones was determined by cholangiography. From August 1979, ultrasonography was performed to determine the presence/absence of gall bladder stones.

Abbreviations: EPT, endoscopic papillotomy; GB, gall bladder; RR, relative risk.

Figure 1 Patient classification according to gall bladder status. *The reasons were acute cholecystitis (three patients) or asymptomatic (38 patients). †Median duration from prior cholecystectomy to endoscopic papillotomy (EPT) was 6.6 years [95% confidence interval 4.7–8.7].

The presence/absence of pneumobilia was determined by endoscopic retrograde cholangiography taken after extraction of the stones, usually performed within one week of EPT. Pneumobilia was defined as a substantial amount of air in the bile duct that was still visualised despite adequate filling of the bile duct with contrast and that did not dissipate after changes in patient position.

Complications that occurred within one month of EPT were defined as early complications. Early complications were defined in a similar manner to those of “moderate” to “severe” grade suggested by Cotton and colleagues.³

Complications occurring more than one month after EPT were defined as late complications. The diagnosis of recurrent choledocholithiasis was made based on the radiological visualisation of bile duct stones. Cases in which spontaneous bile duct stone passage was strongly suspected were also considered as recurrent choledocholithiasis.

Patients were divided into four groups according to gall bladder status: “acalculous GB” group, “calculous GB” group, “cholecystectomy” group, and “prior cholecystectomy” group (fig 1).

Follow up

Follow up data on biliary complications were obtained by questionnaires, either by mail or telephone, every 2–3 years starting from the time of the initial EPT. In cases where patients required hospitalisation or further medical treatment, the medical records were obtained. Median duration of follow up was 7.5 years (95% CI 7.2–7.8).

Risk factors for recurrence of bile duct stones

The following factors were considered in the evaluation of risk factors for recurrence of bile duct stones as late complications: age, sex, gall bladder status, periampullary diverticulum, number of bile duct stones, diameter of bile duct stones, diameter of the bile duct, lithotripsy, precutting, pneumobilia, and early complications.

Apart from these analyses, differences in stone recurrence rates among the following three periods were analysed: first

period (December 1975 to October 1978; treated with EPT alone); second period (November 1978 to January 1987; treated with EPT and basket extraction); and third period (February 1987 to September 1998; treated with EPT, basket extraction, and lithotripsy).

Statistical analysis

The cumulative stone recurrence rate and cumulative non-recurrence curve were calculated by the Kaplan-Meier method. The Cox proportional hazards model was used to determine the most significant factors related to recurrence. Forward selection and backward elimination stepwise regression procedures based on the likelihood ratio test were used to determine which factors best predicted stone recurrence. Covariations between the factors were checked and if two or more risk factors were strongly intercorrelated, only one factor was included in the model from the highly correlated set.⁴ All p values presented in this study are of the two tailed type. Differences with a p value of <0.05 were considered statistically significant.

RESULTS

Reliable follow up information was obtained for 983 (94.3%) of 1042 patients. These 983 patients (500 men and 483 women; median age 67 years (95% CI 66–68)) were included in the analyses.

Early complications

Early complications included bleeding in 10 patients, pancreatitis in 14 patients, cholangitis in 10 patients, and acute cholecystitis in nine patients. Some patients had more than one complication. Perforation did not occur. One patient, aged 48 years, died of sepsis associated with cholecystitis 12 days after the procedure. Two patients died within 30 days after EPT due to causes unrelated to the procedure. Mortality rate related to the procedure was 0.1%.

Late complications

Acute cholecystitis occurred in 37 patients (three in the “acalculous GB” group, 34 in the “calculous GB” group). New stone

formation in the gall bladder had been confirmed prior to the onset in all former three patients. Elective cholecystectomy was performed in 27 of 37 patients.

Recurrence of bile duct stones was detected in 111 patients (107 confirmed radiologically, four considered to be spontaneous bile duct stone passage). In these 111, cholangitis concurred with recurrence in 14 patients. Among these 14 patients, two developed a liver abscess. Recurrence developed multiple times in 18 patients (twice in 10 patients, three or more than twice in eight patients). Median length of time until recurrence was 3.9 years (95% CI 3.0–5.1). The cumulative recurrence rates at five years, 10 years, 15 years, and 20 years in patients overall were 8.5% (95% CI 6.5–10.5), 12.5% (95% CI 10.0–15.0), 19.1% (95% CI 15.0–23.2), and 24.2% (95% CI 17.9–30.5), respectively.

Cause of death

During follow up, 297 of 983 patients died. Median age at death was 81 years (95% CI 80–82). One patient, aged 77 years, died of acute obstructive suppurative cholangitis resulting from recurrent bile duct stones six months after EPT. This patient was unable to obtain prompt medical care at the onset of cholangitis because of general paralysis as a sequela of a cerebrovascular accident. This was the only patient who died due to gall stone disease. Eighteen patients died from pancreaticobiliary malignancy (bile duct carcinoma in three, intrahepatic cholangiocarcinoma in one, pancreatic carcinoma in seven, gall bladder carcinoma in six). All patients who died from gall bladder carcinoma belonged to the “calculous GB” group.

Univariate analysis

The results of univariate analysis for recurrence of bile duct stones in relation to each factor are given in table 1.

The “acalculous GB” group was less prone to stone recurrence than the “prior cholecystectomy” group and the “calculous GB” group (fig 2). The need for lithotripsy was associated with significant increases in recurrence rates (fig 3). The presence/absence of pneumobilia (fig 4), diameter of the bile duct, and diameter of the bile duct stones tended to affect recurrence rate but they did not reach statistical significance.

Among 11 variables, strong intercorrelations were observed between lithotripsy, the diameter of the bile duct, and the diameter of bile duct stones (table 2). To address the potential effects of the former on the latter two, the data were reanalysed with 453 patients who were treated before February 1987, the period for which lithotripsy had not yet been introduced (table 3). Without the influence of lithotripsy, the diameter of the bile duct and the diameter of bile duct stones were not associated with stone recurrence.

Stone recurrence rates observed in the three periods are given in table 4. There were no significant differences.

Multivariate analysis

The diameter of the bile duct and diameter of bile duct stones were considered to be dependent variables of lithotripsy; only lithotripsy was incorporated into the stepwise regression analysis. Forward selection and backward elimination stepwise regression procedures led to the same final model

Table 1 Univariate analysis for recurrence of bile duct stones

Variable	n*	Recurrence	Recurrence rate (%)			RR	(95% CI)	p Value
			5 y	10 y	15 y			
Age								
<65 y	418	47	6.8	11.6	16.4	1		
≥65 y	565	64	9.8	13.1	22.9	1.35	(0.92–1.98)	0.12
Sex								
Male	500	59	10.0	14.0	19.1	1		
Female	483	52	7.0	11.1	19.1	0.82	(0.56–1.19)	0.30
GB status								
Acalculous GB	246	16	3.9	7.6	11.3	1		
Calculous GB	448	50	9.7	14.5	23.9	2.10	(1.20–3.70)	0.0098
Cholecystectomy	41	1	0.0	0.0	7.1	0.35	(0.05–2.60)	0.30
Prior cholecystectomy	248	44	11.8	16.1	22.9	2.34	(1.32–4.16)	0.0037
Diverticulum								
Absent	623	70	8.0	12.0	18.5	1		
Present	343	39	9.6	13.4	20.7	1.09	(0.74–1.62)	0.66
Duct diameter								
<11 mm	139	9	3.4	7.7	14.3	1		
≥11 mm	802	98	9.4	13.7	20.8	1.97	(0.99–3.90)	0.052
No of stones†								
1	505	57	9.0	12.5	18.2	1		
≥2	414	51	8.7	13.2	21.3	1.14	(0.78–1.66)	0.50
Stone diameter†								
<11 mm	518	53	6.5	11.5	17.5	1		
≥11 mm	394	54	11.9	14.4	22.6	1.46	(0.99–2.13)	0.052
Lithotripsy								
No	796	83	6.7	11.0	17.5	1		
Yes	187	28	16.6	19.4	-	2.19	(1.41–3.41)	0.0005
Precutting								
No	911	102	8.6	12.5	18.5	1		
Yes	72	9	7.4	13.1	25.9	1.20	(0.61–2.38)	0.60
Pneumobilia								
Absent	762	73	7.3	10.4	17.0	1		
Present	178	30	10.8	18.6	25.4	1.49	(0.97–2.28)	0.069
Early complications								
No	944	107	8.3	12.6	19.4	1		
Yes	39	4	12.8	12.8	12.8	0.88	(0.32–2.39)	0.80

*Data were missing for less than 5% for the following variables: diverticulum (missing in 17), bile duct diameter (missing in 42), number of stones (missing in four), stone diameter (missing in 11), pneumobilia (missing in 43).

†Bile duct stones were not visualised on endoscopic retrograde cholangiography in 60 cases.

EPT, endoscopic papillotomy; GB, gall bladder; RR, relative risk; CI, confidence interval.

No at risk

Acalculous GB	246	150	86	29	4
Calculous GB	448	231	90	22	3
Prior cholecystectomy	248	163	109	58	13

Figure 2 Kaplan-Meier curves showing the rate of stone non-recurrence in patients classified according to gall bladder status (the "cholecystectomy" group is not included in this figure). EPT, endoscopic papillotomy.

No at risk

Lithotripsy not required	796	498	276	114	21
Lithotripsy required	187	78	23	—	—

Figure 3 Kaplan-Meier curves showing the rate of stone non-recurrence in patients requiring or not requiring lithotripsy. EPT, endoscopic papillotomy.

No at risk

Pneumobilia not visualised	762	440	215	74	8
Pneumobilia visualised	178	112	72	36	8

Figure 4 Kaplan-Meier curves showing the rate of stone non-recurrence in patients with or without pneumobilia. EPT, endoscopic papillotomy.

that consisted of three factors (gall bladder status, lithotripsy, and pneumobilia) (table 5). All of these factors reached statistical significance. For each gall bladder status group, the number of patients who required lithotripsy and the number of patients who had pneumobilia are given in table 6.

Table 2 Covariations between lithotripsy, bile duct diameter, and stone diameter

	Bile duct diameter		Stone diameter	
	<11 mm	≥11 mm	<11 mm	≥11 mm
Lithotripsy				
No	134	621	488	237
Yes	5	181	30	157
	p<0.0001*		p<0.0001†	

*Fisher's exact test

† χ^2 test with Yates' correction.

Table 3 Univariate analysis for recurrence of bile duct stones in 453 patients who were treated before February 1987

Variable	RR	95% CI	p Value
Duct diameter			
<11 mm	1		
≥11 mm	0.94	0.44–2.01	0.878
Stone diameter			
<11 mm	1		
≥11 mm	0.96	0.55–1.67	0.881

RR, relative risk; CI, confidence interval.

DISCUSSION

Among the many long term follow up studies on post-EPT patients, several authors attempted to analyse the relationship between risk factors and recurrence of bile duct stones.^{5–10} Some also addressed predictive factors for recurrence of bile duct stones.^{6–10} Wojtun and colleagues⁶ reviewed 324 post-EPT patients after a mean follow up of six years and reported that patients with concurrent cholecystolithiasis and choledocholithiasis were at a higher risk of developing recurrent stones. Pereira-Lima and colleagues⁷ evaluated 203 post-EPT patients after a mean follow up of 6.2 years and reported that a bile duct greater than 15 mm in diameter and periampullary diverticulum were associated with recurrent stones. A previous report of ours indicated that lithotripsy and pneumobilia were predisposing factors for stone recurrence among patients with concurrent choledocholithiasis and cholecystolithiasis.¹⁰

In general, it is difficult to detect significant risk factors for recurrent bile duct stones for the following reasons. Firstly, follow up is difficult because most patients become free from symptoms and leave medical institutions. Secondly, a large number of patients must be followed up for a long period to carry out a statistical analysis.¹¹ The power of Cox proportional hazards model depends largely on the number of end points in the data set.¹² Most of these follow up studies involved a small sample of patients followed for a short period of time.

Compared with previously published reports, ours is the largest study to date, with a median follow up of 7.5 years and sufficient statistical power.

However, as the present survey was carried out over three decades, it may have potential limitations due to improvement both in endoscopic procedures and imaging techniques. The success rates of EPT and bile duct stone extraction have been improved in these decades,¹³ and thus there are certain selection biases regarding patients included in this study. But it is remarkable that the stone recurrence rate did not vary significantly over these three decades.

Early complications were observed in 4.0% of all cases. This value is low compared with that in other studies,^{3–15} and one possible explanation could be differences in the criteria used to define each complication.

Table 4 Stone recurrence rates observed in the three time periods (see text for details)

	n	Recurrence	Recurrence rate (%)			RR	(95% CI)	p Value
			5 y	10 y	15 y			
First period	69	8	5.5	15.5	18.9	1		
Second period	367	47	6.3	9.8	17.7	1.11	(0.52–2.35)	0.79
Third period	547	56	10.1	14.3	—	1.51	(0.71–3.22)	0.29

*RR, relative risk; CI, confidence interval.

Table 5 Multivariate analysis for recurrence of bile duct stones

Variables	RR	95% CI	p Value
GB status			
Acalculous GB	1		
Calculous GB	2.16	1.21–3.87	0.0093
Cholecystectomy	0.44	0.06–3.33	0.42
Prior cholecystectomy	2.26	1.24–4.14	0.0078
Lithotripsy			
No	1		
Yes	2.37	1.47–3.81	0.0004
Pneumobilia			
Absent	1		
Present	1.57	1.01–2.43	0.044

GB, gall bladder; RR, relative risk; CI, confidence interval.

Table 6 Number of patients who had lithotripsy and pneumobilia in each gall bladder status group

	Lithotripsy		Pneumobilia	
	No	Yes	No	Yes
Acalculous GB	192	54	196	37
Calculous GB	351	97	363	70
Cholecystectomy	39	2	37	3
Prior cholecystectomy	214	34	166	68

GB, gall bladder.

The incidence of bile duct stone recurrence during follow up was 11.3%, which is comparable with that in other studies.^{5–9 13 16}

Recurrence was observed many times in 1.8% of all cases. In these patients, bile duct stones developed three or more times in 44%. Therefore, patients in whom bile duct stones recurred twice should be carefully followed up and surveillance endoscopic retrograde cholangiography was recommended.

In the multivariate analysis, we found that gall bladder status, lithotripsy, and pneumobilia were significantly related to recurrence.

Bile duct stones most commonly have their origin in the common bile duct as primary stones rather than in the gall bladder with secondary descent into the bile duct.¹⁷ All recurrent stones in the “acalculous GB” group and the “prior cholecystectomy” group were considered to be primary bile duct stones.^{17 18} Why these two groups were different in terms of recurrence rate is debatable. Comparing the “acalculous GB” group with the “prior cholecystectomy” group, it was probable that gall bladder motility was related to the low recurrence rate of the former group. Several authors proved that significant improvement in gall bladder motility was observed after EPT.^{19–22} It was also noted that bile stasis was an important factor in the pathogenesis of bile duct stone formation.^{16 17 23} Frossard and colleagues²⁴ evaluated 92 patients with choledocholithiasis and reported that the presence

of the gall bladder was significantly associated with spontaneous bile duct stone passage. Gall bladder without gall stones after EPT is considered to wash away bile and prevent new stone formation or flush out newly produced stones.

At present, the role of EPT in patients with an intact gall bladder without stones is still controversial. Whether these patients should undergo cholecystectomy after successful endoscopic stone extraction is also a matter of controversy. Since patients of this type are not uncommon in Eastern countries, these problems should be resolved. Considering the low rate of recurrent bile duct stones, the low risk of developing acute cholecystitis, and no occurrence of gall bladder carcinoma, patients with choledocholithiasis who have an intact gall bladder without cholecystolithiasis are suitable for EPT and their gall bladder has to be left in situ after EPT.

Comparing the “acalculous GB” group with the “calculous GB” group, the difference in recurrence rate was probably due to the fact that choledocholithiasis in the latter group might have derived from cholecystolithiasis in a considerable number of patients. The fact that the relative risk of the “cholecystectomy” group was lower than that of the “calculous GB” group implied that once the gall bladder was removed the recurrence rate would decrease.

Although the “calculous GB” group was more prone to recurrence of stones, its relative risk was almost equivalent to that of the “prior cholecystectomy” group. Also, acute cholecystitis was not particularly frequent during follow up. Therefore, the decision to perform cholecystectomy should be made by the physician and the patient after considering all potential risks, including complications associated with leaving or removing the gall bladder.¹⁰ All patients should deserve the opportunity to accept or deny the removal of their gall bladder.

Lithotripsy was also related to the development of recurrent stones. This result was the same as our previous report within the limits of concurrent choledocholithiasis and cholecystolithiasis patients.¹⁰ It is natural that small stone fragments left after lithotripsy may act as nidi for stone recurrence. Therefore, it is important to flush out minute fragments from the bile duct. If small fragments are cleared away from the bile duct completely, recurrence rate may decrease. Recently, intra-ductal ultrasonography has been attempted to confirm clearance of stone fragments.^{25 26}

In the univariate analysis, a bile duct greater than 10 mm in diameter and bile duct stones greater than 10 mm in diameter tended to increase the recurrence rate. This result is similar to that reported by Pereira-Lima and colleagues,⁷ but our interpretation differs from theirs. A stone greater than 10 mm existed in the large bile duct and was usually treated with lithotripsy. Therefore, it is reasonable to believe that the diameter of the bile duct and the diameter of the bile duct stones are strongly correlated with lithotripsy. In other words, these two factors were not independent variables and only seemed to be prognostic factors under the strong influence of lithotripsy. In patients who were treated in the period when mechanical lithotripsy was not introduced, the diameter of the bile duct and diameter of bile duct stones were not associated with stone recurrence. The result of this reanalysis is consistent with our view.

Similar to our previous report, we found that the presence of pneumobilia immediately after EPT influenced the frequency of stone recurrence. The mechanism of how pneumobilia relates to stone recurrence is unclear. But it is unquestionable that pneumobilia is equivalent to a condition where reflux of duodenal contents into the bile duct occurs with ease. Duodenobiliary reflux results in bile infection and bile infection plays an essential role in the formation of brown pigment stones.^{23 27 28 29} Also, loss of function of the biliary sphincter after EPT is related to duodenobiliary reflux.³⁰ The function of the biliary sphincter may be associated with stone recurrence.

In conclusion, the "acalculous GB" group was less prone to bile duct stone recurrence than the "prior cholecystectomy" group and the "calculous GB" group. The gall bladder left in situ without gall stones after EPT was considered to wash away bile and prevent the formation of new stones or flush out newly produced stones. Also, lithotripsy should increase stone recurrence. Small stone fragments after lithotripsy may act as nuclei for stone formation. Pneumobilia also seemed to influence the frequency of stone recurrence. Loss of function of the biliary sphincter may be related to this mechanism.

For early detection of recurrent choledocholithiasis, patients who belong to the "prior cholecystectomy" or "calculous GB" group at the time of the initial EPT should be carefully followed up. The same is recommended for patients who need lithotripsy or are found to have pneumobilia at the time of initial EPT. In particular, for patients who present more than one of these conditions, periodic surveillance by means of blood tests, ultrasonography, and/or magnetic resonance cholangiography may be recommended.

To avoid recurrent choledocholithiasis, clearance of stone fragments should be confirmed after lithotripsy.

The finding of our study on gall bladder status provides reliable evidence that patients who have their gall bladder without gall stones should be treated with an endoscopic procedure alone.

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