Remaining issues of recommended management in current guidelines for asymptomatic common bile duct stones

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Abstract

Current guidelines for treating asymptomatic common bile duct stones (CBDS) recommend stone removal, with endoscopic retrograde cholangiopancreatography (ERCP) being the first treatment choice. When deciding on ERCP treatment for asymptomatic CBDS, the risk of ERCP-related complications and outcome of natural history of asymptomatic CBDS should be compared. The incidence rate of ERCP-related complications, particularly of post-ERCP pancreatitis for asymptomatic CBDS, was reportedly higher than that of symptomatic biliopancreatic diseases. Although studies have reported short- to mid-term outcomes of natural history of asymptomatic CBDS, its long-term natural history is not well known. Till date, there are no prospective studies that determined whether ERCP has a better outcome than no treatment in patients with asymptomatic CBDS or not. No randomized controlled trial has evaluated the risk of early and late ERCP-related complications vs the risk of biliary complications in the wait-and-see approach, suggesting that a change is needed in our perspective on endoscopic treatment for asymptomatic CBDS. Further studies examining long-term complication risks of ERCP and wait-and-see groups for asymptomatic CBDS are warranted to discuss...
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INTRODUCTION

Common bile duct stones (CBDS) are a common biliary tract disease worldwide with secondary CBDS migrated from gallbladder into CBD, being one of major causes of CBDS [1]. The prevalence of gallstones has increased in the elderly population [2], and for this reason, the number of patients with CBDS is likely to increase in the future as the world’s population ages. Owing to diagnostic modalities, such as computed tomography (CT), endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP) recently developed, there is greater probability for asymptomatic CBDS to be discovered incidentally.

Endoscopic management by endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as a first choice of treatment for CBDS [3]. For asymptomatic CBDS, endoscopic treatment is consistently recommended in current guidelines [1,3-5], and removal of asymptomatic CBDS is a common practice as asymptomatic CBDS have a potential risk of causing obstructive jaundice, acute cholangitis, and biliary pancreatitis.

ERCP is however an endoscopic procedure with high risk of procedure-related complications. In general, an overall incidence of ERCP-related complications, including post-ERCP pancreatitis (PEP), cholangitis, bleeding, and perforation has been reported in 4.0%-15.9% of patients [6,7], PEP being the most common. A systematic review of randomized controlled trials revealed an overall PEP incidence of 9.7% [6].

When determining the indication of ERCP for asymptomatic CBDS, the risk of ERCP-related complications should be focused on asymptomatic CBDS rather than on average risk of ERCP-related complications of biliopancreatic diseases.

Some investigators recently reported the risk of ERCP-related complications focusing on asymptomatic CBDS. An overall incidence rate of ERCP-related complication for asymptomatic CBDS was reported to be approximately 15%-25%, with a PEP incidence of approximately 12%-20% [9-13]. The risk of ERCP-related complications, in particular the risk of PEP, for asymptomatic CBDS appeared to be higher than that previously reported. The risk of ERCP-related complications for asymptomatic common bile duct (CBD) should therefore not be the same as the previously reported risk of ERCP-related complications for biliopancreatic diseases.
When determining the indication of ERCP for asymptomatic CBDS, the risk of biliary complications in wait-and-see approach should be considered. Previous studies on the natural history of CBDS reported the biliary complication rates of wait-and-see approach for asymptomatic CBDS to vary between 0-25.3% during a follow-up period of 30 d to 4.8 years[14-18]. Endoscopic sphincterotomy, endoscopic papillary balloon dilation, or endoscopic large papillary balloon dilation was performed for endoscopic stone removal bearing in mind the risk of stone recurrence as these procedures can cause papillary dysfunction[19,20].

We clarified the remaining issues of recommended management in current guidelines for asymptomatic CBDS by reviewing the current guidelines for asymptomatic CBDS and previous studies on the risk of ERCP-related complications and natural history of asymptomatic CBDS.

**EPIDEMIOLOGY OF CBDS**

The origin of CBDS is different in Asian populations and Western population. Primary CBDS, which are more common in Asian populations, form de novo in the intra- and extrahepatic ducts. Primary CBDS are associated with biliary infection and cholestasis[21-24]. Secondary CBDS, which are more prevalent in Western populations, typically originate in the gallbladder and migrate into CBD[1].

The prevalence of CBDS in patients with symptomatic gallstones is estimated to be 10%-20%[25-29]. In patients without jaundice and dilated CBD on trans-abdominal ultrasound, the prevalence of CBDS during cholecystectomy is reported to be <5%[15]. It has been reported that the rate of coexisting CBDS was increased in elderly populations with symptomatic gallstones[2].

However, to best of our knowledge, there are no studies focusing on the prevalence of CBDS in patients with asymptomatic gallstones, as most studies are based on intraoperative cholangiography during cholecystectomy for symptomatic gallstones. Although the prevalence of CBDS is expected to increase due to the aging of world population, the prevalence of CBDS is still unknown.

Further studies are warranted to clarify the prevalence of asymptomatic CBDS for a better understanding of the natural history of asymptomatic CBDS.

**DIAGNOSTIC MODALITIES OF CBDS**

Recent guidelines recommend the use of either EUS or MRCP to diagnose CBDS in patients with suspected CBDS. A recent meta-analysis of five head-to-head studies revealed that the sensitivity and specificity of EUS and MRCP are 97% vs 90%, and specificity 87% vs 92%, respectively. However, the overall diagnostic odds ratio of EUS was significantly higher than that of MRCP because EUS had a higher detection rate of small CBDS compared with that of MRCP, while the specificity showed no significant differences between the two modalities[30]. Another meta-analysis demonstrated high diagnostic accuracy for EUS and MRCP. This meta-analysis reported that the sensitivity and specificity for EUS were 95% and 97%, and 93% and 96% for MRCP[31].

Although CT is a diagnostic modality for CBDS, routine CT scanning for suspected CBDS is not recommend in current guidelines because of some disadvantages, such as radiation exposure, side effects of contrast agent, and lower diagnostic ability for CBDS compared with MRCP and EUS[3,32]. Several studies examining the diagnostic ability of multi-slice CT scanner for CBDS showed that conventional CT scanning had reasonable sensitivity (69%-87%) and specificity (68%-96%) for diagnostic CBDS[33-36]. Recently, dual-energy CT scanner and dual-layer spectral CT (DLCT) scanner, which can perform a multiparameter approach, are commercially available. These CT scanners can detect noncalcified stones, which cannot be detected in conventional CT. A recent retrospective study comparing the diagnostic ability between DLCT and modern MRCP suggested that the diagnostic ability of DLCT for biliary stones was comparable to that of modern MRCP[37]; the detection of noncalcified small stones < 9 mm in diameter seem to be a limitation of dual-energy CT and DLCT scanners[37-39].

Diagnostic modalities for CBDS, such as EUS, MRCP, and CT have recently been developed increasing the chance of detecting incidentally discovered asymptomatic CBD.
RECOMMENDED MANAGEMENT IN CURRENT GUIDELINES FOR ASYMPTOMATIC CBDS

Recommended management of current guidelines is presented in Table 1. Current guidelines published by European Society of Gastrointestinal Endoscopy, The British Society of Gastroenterology, American Society for Gastrointestinal Endoscopy, and The Japanese Society of Gastroenterology strongly recommend bile duct stone removal[1,3-5], with ERCP as the first choice of treatment for asymptomatic CBDS removal.

Although the lifetime risk of untreated CBDS is unknown, complication of CBDS, such as pain, obstructive jaundice, acute cholangitis, hepatic abscesses, biliary pancreatitis, secondary biliary cirrhosis, and portal hypertension due to biliary obstruction are potentially life threatening. Available guidelines recommend treatment for asymptomatic CBDS. A conservative approach can only be considered in patients in whom the risks of CBDS removal are higher than the risks of leaving CBDS in situ[1,3,4].

Current guidelines strongly recommended stone removal for asymptomatic CBDS even though the evidence quality is low.

RISK OF ERCP-RELATED COMPLICATIONS FOR ASYMPTOMATIC CBDS

It has been recognized that the risk of ERCP-related complications of CBDS was 6%-15%[6,7]. However, the risk of ERCP focusing on asymptomatic CBDS is important to determine the indication of ERCP for asymptomatic CBDS.

Recently, several reports revealed that the risk of ERCP-related complications for patients with asymptomatic CBDS was higher than that for symptomatic patients (Table 2). A multicenter retrospective study including 164 patients with asymptomatic CBDS and 949 patients with symptomatic CBDS reported that the incidence rate of ERCP-related complications was 19.5% in asymptomatic patients and 6.2% in symptomatic patients. In particular, PEP was significantly higher in asymptomatic patients than symptomatic patients (14.6% vs 3.0%)[11]. A prospective study including 53 asymptomatic patients and 274 symptomatic patients reported the similar results. The rate of ERCP-related complications in asymptomatic patients and symptomatic patients were 26.4% vs 11.7%, respectively, and the rate of PEP was 20.8% vs 6.9%, respectively[12]. The possible explanation for a higher incidence of PEP in asymptomatic patients is that the number of asymptomatic patients with normal serum bilirubin, nondilated CBD, and difficult cannulation, which are patient- and procedure-related risk factors of PEP, was higher than that of symptomatic patients because of no cholestasis in patients with asymptomatic CBDS. Furthermore, asymptomatic CBDS itself may be an important clinical risk factor of PEP[11].

Although a single-center retrospective study, in which ERCP was performed by skilled endoscopists, reported that the incidence of both overall ERCP-related complications and PEP in asymptomatic patients were comparable with those of symptomatic patients[13], other studies reported that the incidence rate of overall ERCP-related complication was approximately 15%-25% in asymptomatic patients and 4%-12% in symptomatic patients, and the incidence of PEP was approximately 12%-20% in asymptomatic patients and 2%-7% in symptomatic patients[9-12]. Therefore, the risk of ERCP-related complications, in particular the risk of PEP, in asymptomatic patients with CBDS is possibly higher than that of symptomatic patients.

NATURAL HISTORY OF ASYMPTOMATIC CBDS

About 2%-4% of patients with asymptomatic gallstones becomes symptomatic over the years. Multiple gallstones, negative cholecystography findings, and young age are the risk factors for transition from asymptomatic to symptomatic[40-43]. The potential risk of intraoperative and postoperative complications related to surgery explains why current guidelines are against laparoscopic cholecystectomy for patients with asymptomatic gallstones in a normal gallbladder[4,32].

Although the long-term natural history of CBDS is less understood than that of gallstones, several studies have examined the short- to middle-term natural history of asymptomatic CBDS[14-18] (Table 3).
Table 1 Recommended management and evidence level in current guidelines for asymptomatic common bile duct stones

| Guideline | Recommendation |
|-----------|----------------|
| ESGE[1]   | ESGE recommends stone extraction in all patients with CBDS, regardless of being symptomatic or not, who are fit enough to tolerate the intervention. (Strong recommendation, low quality evidence) |
| BSG[3]    | Stone extraction is recommended in patients diagnosed with CBDS if possible. Evidence of benefit of stone extraction is greatest for symptomatic patients (Low quality evidence; strong recommendation) |
| JGES[4]   | Asymptomatic choledocholithiasis should be treated because of a risk of developing biliary complications. [Evidence level: A; Strength of recommendation (agreement rate): 2 (100%)] |
| ASGE[5]   | CBDS should be treated if detected regardless of the presence or absence of significant mitigating clinical circumstances (Moderate quality) |

CBDS: Common bile duct stones; ESGE: European Society of Gastrointestinal Endoscopy; BSG: The British Society of Gastroenterology; ASGE: American Society for Gastrointestinal Endoscopy; JSGE: The Japanese Society of Gastroenterology.

Table 2 Summary of studies comparing the risks of endoscopic retrograde cholangiopancreatography-related complications for asymptomatic and symptomatic patients with common bile duct stones

| Ref.          | Study design               | Patients, n  | Overall, complications (%) | PEP (%) |
|---------------|----------------------------|--------------|----------------------------|---------|
|               |                            | Asymptomatic | Symptomatic                | Asymptomatic | Symptomatic  | Asymptomatic | Symptomatic  |
|               |                            | group        | group                      | group    | group        | group        | group        |
| Kim et al[9], 2016 | Single-center retrospective   | 32           | 536                        | 15.6     | 10.4         | 12.5<sup>a</sup> | 3.9         |
| Saito et al[10], 2017 | Multicenter retrospective             | 67           | 536                        | 26.9<sup>a</sup> | 3.9         | 16.4<sup>a</sup> | 2.2         |
| Saito et al[11], 2019 | Multicenter retrospective             | 164          | 949                        | 19.5<sup>a</sup> | 6.2         | 14.6<sup>a</sup> | 3.0         |
| Xu et al[12], 2019 | Single-center prospective             | 53           | 274                        | 26.4<sup>a</sup> | 11.7        | 20.8<sup>a</sup> | 6.9         |
| Xiao et al[13], 2021 | Single-center retrospective             | 79           | 795                        | 13.3     | 9.7          | 7.6          | 6.9         |

<sup>a</sup>Statistically significant difference. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Postendoscopic retrograde cholangiopancreatography pancreatitis.

Table 3 Summary of studies reporting natural history of asymptomatic common bile duct stones

| Ref.          | Study design | Patients, n | Median follow-up period | Cumulative incidence of biliary complications, n (%) |
|---------------|--------------|-------------|-------------------------|-----------------------------------------------|
| Ammori et al[14], 2000 | Prospective   | 14          | 1.4 yr                  | 4 (29)                                        |
| Collins et al[15], 2004 | Prospective   | 46          | 6 wk                    | 0                                             |
| Caddy et al[16], 2005 | Retrospective | 59          | 4.8 yr                  | 0                                             |
| Moller et al[17], 2014 | Retrospective | 594         | 30 d                    | 150 (25)                                      |
| Hakuta et al[18], 2020 | Retrospective | 114         | 3.2 yr                  | 20 (18)                                       |

Data from the GallRiks study, including 594 patients who had CBDS incidentally discovered by intraoperative cholangiography and were untreated, suggest that 25.3% (150/594) of patients developed unfavorable outcomes defined as incomplete clearance of CBDS and/or complications within 30 d post cholecystectomy. Among the 3234 patients who underwent any procedure of CBDS removal, including post- or intraoperative ERCP, laparoscopic or open cholecystotomy, transcystic stone extraction, or flushing/manipulation, 12.7% (411/3234) developed unfavorable
outcomes. This led to conclusion that if CBDS are detected, they should be removed to reduce the risk of CBDS-related complications over time\[17\].

However, there are several noteworthy aspects in the results of GallRiks study. First, long-term outcomes of patients in the untreated asymptomatic CBDS group and treated asymptomatic CBDS group were unclear. Second, patients who underwent postoperative ERCP had a high unfavorable outcome rate of 18% (103/572), suggesting that ERCP for asymptomatic CBDS had a high risk of ERCP-related complications. Third, although the unfavorable outcome rate of no treatment for CBDS also included post-ERCP complications in patients who became symptomatic and underwent ERCP within 30 d post cholecystectomy, this unfavorable outcome should also be included in the unfavorable outcomes of treatment strategies. Therefore, the risk of ERCP-related complications for CBDS removal may be underestimated in the GallRiks study.

Hakuta et al\[18\] recently reported that out of the 114 patients with asymptomatic CBDS who underwent wait-and-see approach, 18% developed CBDS-related complications, which were cholangitis in 16 patients (14%), cholecystitis in 1 patient (0.9%), and cholestasis in 4 patients (3.5%), and no biliary pancreatitis during the average follow-up period of 3.2 years.

In some patients with asymptomatic small CBDS, the stones can be drained into duodenum spontaneously without the need for an intervention\[44-48\]. Collins et al\[15\] demonstrated the spontaneous passage of small CBDS without serious complications in 24 of 46 patients with a filling defect observed by intraoperative cholangiography during cholecystectomy within 6 wk of surgery. Asymptomatic spontaneous passage of small CBDS less than 8 mm in size has also been found in approximately 20% CBDS in the interval between diagnosis at EUS and ERCP\[49\].

Clarifying the long-term natural history of asymptomatic CBDS is essential to determine whether intervention by ERCP or wait-and-see approach for asymptomatic CBDS has a better outcome. A large-scale prospective study examining long-term natural history of asymptomatic CBDS is therefore warranted.

### RECURRENT OF CBDS AFTER ENDOSCOPIC STONE REMOVAL

The Korean nationwide study including 46181 patients with CBDS demonstrated that 5228 (11.3%) patients experienced first CBDS recurrence at mean follow-up of 4.3 years. The cumulative second and third recurrence rates after the initial CBD recurrence were 23.4% and 33.4%. Therefore, the higher the frequency of recurrence of stones, the higher the the recurrence rate of the stones\[19\]. Another retrospective study revealed that CBDS recurrence was observed in 121 patients (12.4%) out of 976 patients. Multiple recurrence after first recurrence was observed in 26 patients (21.5%) of 121 patients with stone recurrence during a median follow-up period of 5.1 years. The risk factors for single recurrence were CBD size, gallbladder left in situ with gallstones, and pneumobilia after ERCP, and the risk factor for multiple recurrence was the number of CBDS at the first recurrence\[20\].

Stone recurrence should be considered when balancing stone removal by ERCP vs wait-and-see approach for asymptomatic CBDS.

### REMAINING ISSUES IN CURRENT GUIDELINES FOR ASYMPTOMATIC CBDS

When determining the indication of ERCP for patient with asymptomatic CBDS, the risk of early and late ERCP-related complications and long-term natural history of asymptomatic CBDS should be considered.

Recently, the risk of ERCP-related complications for asymptomatic CBDS and the short- to middle-term natural history of this disease have been reported as above\[9-18\].

Based on the previous reports, the risk of early ERCP-related complications, including PEP, cholangitis, bleeding, and perforation can be estimated to approximately 15%-25% with the incidence of PEP of 12%-20% in patients with asymptomatic CBDS\[9-14\]. The risk of late ERCP-related complications including stone recurrence and cholangitis can be estimated to approximately 10%\[18-20\], with the risk of early and late ERCP-related complications for asymptomatic CBDS being approximately 25%-35%. The risk of biliary complications in wait-and-see approach during median follow-up period of 30 d to 4.9 years was estimated to be approximately 0%-
25%[14-18]. ERCP for asymptomatic CBDS may therefore have poorer outcomes than that of wait-and-see approach. A retrospective longitudinal cohort study revealed that out of 77 who underwent ERCP, 16 patients (21%) experienced PEP and 25 patients (32%) experienced early ERCP-related complications and late biliary complications, such as cholangitis and cholecystitis; further, recurrence of CBDS was observed in 7 patients (9.6%) out of 73 patients during a median follow-up period of 1.9 years. They reported that out of the 114 patients with asymptomatic CBDS who underwent wait-and-see approach, 18% developed CBDS-related complications, among which 16 patients (14%) developed cholangitis, 1 patient (0.9%) developed cholecystitis, 4 patients (3.5%) developed cholestasis, and no patients developed biliary pancreatitis during an average follow-up period of 3.2 years. The outcome of intervention group by ERCP was poorer than that of wait-and-see group for patients with asymptomatic CBDS[18].

The fact that there are no randomized prospective studies to compare the risk of ERCP and wait-and-see approach for asymptomatic CBDS is a serious issue as it is important to determine the indication of ERCP for asymptomatic CBDS. Although current guidelines for asymptomatic CBDS recommend stone removal for asymptomatic CBDS, the risk of ERCP and the risk of wait-and-see approach for patients with asymptomatic CBDS cannot be balanced currently because of the absence of randomized controlled studies. Patients should be told that current guidelines' recommendation is to undergo stone extraction in patients with asymptomatic CBDS based on the evidence from the symptomatic patients and expert opinion[1,3].

Further large-scale prospective studies comparing the risk of ERCP and the risk of wait-and-see approach for patients with asymptomatic CBDS are warranted. The indication for preoperative or postoperative ERCP for cholelithiasis should equally be discussed after clarifying the risk and benefit of ERCP for asymptomatic CBDS.

**STRATEGY OF ERCP FOR ASYMPTOMATIC CBDS TO REDUCE ERCP-RELATED COMPLICATIONS**

Because asymptomatic CBDS are a benign disease with no noticeable symptoms, endoscopists must try to reduce ERCP-related complications particularly when performing ERCP for asymptomatic CBDS. A previous study reported that precut sphincterotomy, biliary sphincter dilation, and involvement of trainees were significant risk factors for developing PEP in asymptomatic CBDS[50]. A propensity-score matched study reported that ERCP for asymptomatic CBDS conducted by experienced endoscopists was of comparable safety as ERCP for symptomatic CBDS[13]. ERCP for asymptomatic CBDS should therefore be performed by experienced endoscopists. Prophylactic procedure such as prophylactic pancreatic stent placement should be considered in asymptomatic patients with risk factors of PEP including precut sphincterotomy and biliary sphincter dilation[50].

Single-stage CBDS removal following endoscopic sphincterotomy at first ERCP session in patients with mild-to-moderate cholangitis is accepted in the revised Tokyo guidelines for the management of acute cholangitis and cholecystitis[51], making patients with asymptomatic CBDS a candidate for single-stage CBDS removal. A retrospective study revealed that single-stage CBDS removal with difficult biliary cannulation requiring > 15 min is a significant risk factor of PEP. It may be preferable to remove CBDS at second session ERCP in asymptomatic patients requiring > 15 min for biliary cannulation in order to reduce the development of PEP[52].

**CONCLUSION**

Although current guidelines for asymptomatic CBDS recommend stone removal for asymptomatic CBDS, there is need for a change in perspective on ERCP for asymptomatic CBDS. To best of our knowledge, no prospective studies exist as to whether ERCP has a better outcome than no treatment in patients with asymptomatic CBDS. The risk of inducing early and late ERCP-related complications vs the risk of complication related to the natural history of asymptomatic CBDS cannot be balanced currently.

Further studies examining long-term complication risks of ERCP group and wait-and-see group is warranted to discuss whether routine treatment of asymptomatic CBDS is justified or not.
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