

Endoscopic ultrasound versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a randomized trial comparing two management strategies

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Background and study aims: Diagnostic endoscopic retrograde cholangiography (ERC) is being replaced by endoscopic ultrasonography (EUS) in patients with suspected bile duct stones. The assumption that such an approach is advantageous, however, has never been tested in a randomized trial.

Patients and methods: 100 patients with intermediate probability of bile duct stones were randomly allocated to EUS or ERC. Two patients in the ERC group were excluded; the remaining 98 patients received the allocated intervention and were entered into the analysis (EUS, 50 patients; ERC, 48 patients). Detected stones were removed endoscopically; patients without stones were followed for 1 year. The primary end point was the proportion of patients with a negative outcome, related to either endoscopic procedures (complications) or to false-negative diagnosis of stones. Investigators assessing the negative outcomes were not blinded to group assignment. The secondary end point was the total number of endoscopic procedures (EUS and ERC) performed in each group to diagnose and treat stones.

Results: Bile duct stone prevalence was 28% and 25% in the EUS and ERC groups, respectively ($P > 0.05$). In the EUS group, 71 endoscopic procedures were performed, and 63 in the ERC group (mean per patient, 1.42 ± 0.76 , and 1.31 ± 0.55 , respectively; $P > 0.05$). In the EUS group, these included 49 successful and one failed initial EUS, 15 ERCs for bile duct stone treatment, and six procedures required during follow-up. In the ERC group there were 36 successful and 12 failed initial ERCs, 13 repeat procedures (EUS or ERC) performed after failed or equivocal initial ERC, and two procedures during follow-up. Five patients in the EUS group (10%, 95% CI 4–22) and 19 patients in the ERC group (40%, 95% CI 27–54) experienced a negative outcome ($P < 0.001$). No difference was observed when only moderate to severe complications were considered (6%, 95% CI 1–17, and 10%, 95% CI 4–23, respectively).

Conclusions: In patients with intermediate probability of bile duct stones, the management strategy based on EUS (with selective ERC in patients with confirmed stones) is safer and not associated with an excess of endoscopic procedures compared with a strategy based on ERC alone.

Introduction

Many studies conducted over the last 15 years have consistently shown that diagnosis of bile duct stones by means of endoscopic ultrasonography (EUS) has an accuracy similar to that found with endoscopic retrograde cholangiography (ERC), but without ERC-related morbidity [1–12]. These observations have led to significant changes in the algorithms for management of bile duct stones, with ERC being replaced by EUS, especially in patients with intermediate pre-test probability of disease, in whom stones need to be excluded but safety is a high priority [13,14].

The underlying assumption that such an approach is safer, however, has never been tested in a randomized trial. In addition, previous non-randomized studies have focused strongly on the diagnostic performance of EUS and ERC, rather than on comparison of EUS- and ERC-based management strategies as a whole. Consequently, the following issues have not been taken into account: (i) patients with stones detected on EUS need ERC for treatment, hence ERC-related morbidity is inherent also in the EUS-based strategy; (ii) the number of endoscopic procedures in the EUS-based strategy may be higher because of the need to perform ERC after positive EUS; and

(iii) overlooked stones may cause negative outcomes which, although not directly related to endoscopic procedures, compromise the safety of the management strategy.

To address these issues, we conducted a single-center, open, randomized trial investigating: (i) whether replacing ERC by EUS as the first-line diagnostic tool will improve the safety of management of patients with intermediate probability of bile duct stones; and (ii) the effect of this replacement on the total number of endoscopic procedures needed for diagnosis and treatment of bile duct stones.

Patients and methods



Participants

Consecutive adult patients with clinical suspicion of bile duct stones were included in the study if they met all of the following criteria: (i) estimated baseline probability of stones of no more than 67%, according to the criteria proposed by Barkun et al. (see Appendix, **Table A1**) [15,16]; (ii) no EUS, ERC, or other type of direct cholangiography done within the previous year; (iii) an informed consent in writing to participation in the study. Participants were recruited from inpatients managed at our department over a period of 37 months, from April 1998 through January 2002 (the study was interrupted for 9 months for administrative reasons).

Randomization and interventions

Included patients were randomly assigned, by drawing sealed and consecutively numbered envelopes, to undergo bile duct examination with either EUS or ERC (EUS and ERC groups, respectively). The study investigators were not involved in the preparation of the envelopes with a computer-generated random allocation sequence.

EUS was performed with radial scanning echo endoscopes (Olympus Europe, Hamburg, Germany) as described previously [10], by a single endosonographer whose experience at the beginning of the study included a total of 1163 procedures. ERC, sphincterotomy, and extraction of stones were done in a standard manner with video duodenoscopes (Olympus Europe) by one of two experienced endoscopists (more than 10 years of experience in performing diagnostic and therapeutic ERC). Aggressive cannulation techniques, such as precut sphincterotomy, were not used. Stones detected on EUS were removed endoscopically during a separate session; stones detected on ERC were removed immediately, during the same session. When the initial ERC or EUS failed, a second procedure was carried out. The decision to repeat the same test, or choose another one (EUS after failed ERC, ERC after failed EUS) was left to the discretion of the endoscopist and clinical staff caring for the patient. Patients stayed in the hospital for at least 24 hours post procedure and were monitored for complications (see below).

Follow-up

Patients in whom no stones and no other significant bile duct pathology were detected on initial EUS or ERC were followed for 1 year in order to exclude a false-negative diagnosis. The follow-up involved phone contact with the patient at months 3, 6, 9, and 12, carried out by a study investigator, who assessed the patient using a structured questionnaire about symptoms potentially related to bile duct disorders (attacks of abdominal pain, jaundice, urine/stool discoloration). In addition, the patient was

asked whether he/she had sought medical help, undergone any endoscopic procedure, received parenteral drugs, or been hospitalized due to abdominal problems. Detailed information on the event was obtained if the answer to any of the questions was positive.

In patients with persistent biliary symptoms, the decision to repeat endoscopic examination of the bile duct during the follow-up period was left to the discretion of the patients' physician.

Objective and study end points

The hypothesis that the EUS-based strategy can reduce the rate of negative outcomes without a significant impact on the number of endoscopic procedures required to diagnose and treat bile duct stones, was tested. The primary end point of the study was the proportion of patients with negative outcomes, to related to either endoscopic procedures (complications) or false-negative diagnosis of stones. The secondary end point was the total number of endoscopic procedures performed in order to diagnose and treat stones (or other significant bile duct pathology) in each study group.

Complications of endoscopic procedures were assessed prospectively by a single investigator who was not blinded to group assignment. Severity was graded according to consensus criteria [17,18] as minimal (no need for hospitalization), mild (2–3 days of hospitalization), moderate (4–10 days of hospitalization), severe (> 10 days of hospitalization, or surgery, or intensive care unit admission), or fatal. Because all patients were hospitalized, no clear distinction between the first two categories was possible, and they were merged as minimal-to-mild. Acute pancreatitis was defined as a new or worsened abdominal pain which lasted for more than 24 hours, and was accompanied by a serum amylase level greater than three times the upper normal limit [17]. Transient abdominal pain that required medical intervention (face-to-face doctor attention and analgesic/antispasmodic drugs), but subsided within 24 hours and did not cause prolongation of hospital stay, was recorded as a separate category and graded as a minimal-to-mild complication. Bleeding was defined as clinical evidence of hemorrhage, such as melena or hematemesis, with an associated decrease of at least 2 g/dL in hemoglobin concentration, or the need for transfusion [19].

A negative outcome related to false-negative diagnosis of stones was defined as an occurrence of either of the following: (i) detection of bile duct stones during follow-up, or (ii) hospitalization possibly related to bile duct stones but without definite stone confirmation (acute pancreatitis, acute cholangitis, obstructive jaundice).

Stone removal was the reference standard for diagnosis of bile duct stones. The number of endoscopic procedures performed in order to diagnose and treat stones was determined by counting all EUS and all diagnostic and therapeutic ERC examinations performed during the study in each group. Each successful, failed, and repeated procedure was recorded as a separate entry.

Sample size, data management, and statistical analysis

Assuming that the proportion of patients with a negative outcome would be 5% in the EUS group and 22.5% in the ERC group [20], it was estimated that 47 patients should be recruited per group to have an 80% chance of rejecting the hypothesis of no difference at the 0.05 level. To compensate for nonevaluable patients, enrolment of 50 patients per group was planned.

Demographic, clinical, and follow-up data, and data on endoscopic procedures were prospectively entered into a computer

database. Continuous data are expressed as medians with interquartile ranges (IQR). Proportions are given as numbers and percentages. A modified Wald method was used to compute 95% confidence intervals (CIs). Comparisons between groups were made using the Mann–Whitney *U* test or Fisher's exact test when appropriate. The primary analysis was per protocol. All analyses were performed using the Statistica PL package (StatSoft, Kraków, Poland) or an on-line calculator (<http://graphpad.com/quickcalcs>).

For the purpose of calculating the prevalence of bile duct stones, two patients with bile duct or ampullary tumor (one in each group) were treated as if they had stones.

The research proposal was approved by the ethical committee at our institution.

Results

A total of 257 consecutive patients were assessed for eligibility (Figure 1); 100 of them were included and randomly assigned to either the EUS group (*n* = 50) or ERC group (*n* = 50). Baseline clinical characteristics of both groups were comparable (Table 1). Two patients (4%) in the ERC group were discontinued from the study before ERC was performed, due to consent withdrawal (*n* = 1), and exacerbation of coronary heart disease that was deemed a contraindication for endoscopy (*n* = 1). These patients were excluded from the analysis. The remaining 98 patients received the allocated intervention and were entered into the analysis (EUS group, 50 patients; ERC group, 48 patients).

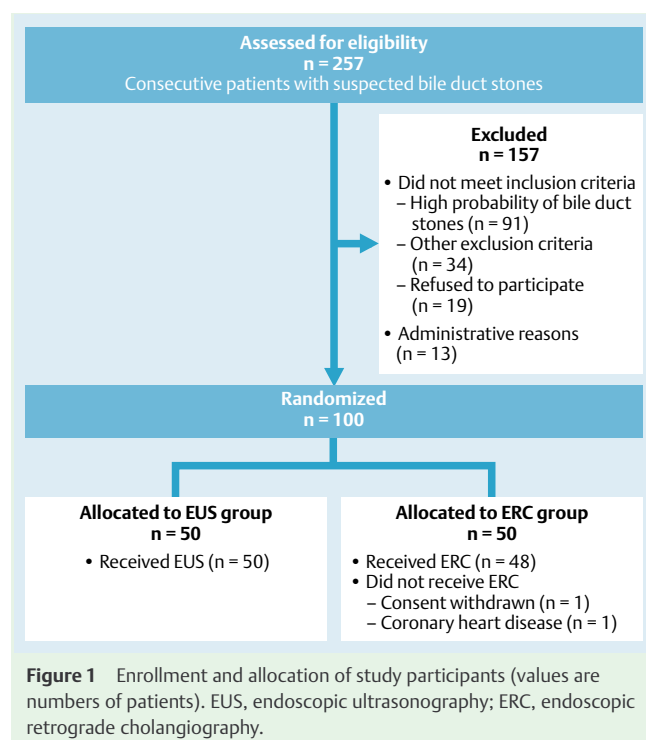


Table 1 Baseline characteristics of study groups

Clinical parameter	EUS group n = 50	ERC group n = 50
Age, median (IQR), years	58 (51–71)	61 (47–68)
Sex, male; female, n (%)	4 (8%); 46 (92%)	8 (16%); 42 (84%)
History of cholecystectomy, n (%)	37 (74%)	31 (62%)
Gallbladder stones present, n (%)	6 (12%)	10 (20%)
Bilirubin level, median (IQR), micromol/L	14.9 (9.3–22.9)	13.7 (10.7–17.6)
Bile duct diameter on abdominal ultrasound, median (IQR), mm	6 (5–9)	6 (5–8)
Number of patients with given risk factor for bile duct stones, n (%)		
Age > 55 years	28 (56%)	30 (60%)
CBD dilatation on abdominal ultrasound*	9 (18%)	8 (16%)
Bilirubin level > 30 micromol/L	3 (6%)	4 (8%)
Bile duct stone on abdominal ultrasound	1 (2%)	0 (0%)

EUS, endoscopic ultrasonography; ERC, endoscopic retrograde cholangiography; IQR, interquartile range; CBD, common bile duct.

P > 0.05 for all parameters (Fisher exact test or Mann–Whitney *U* test as appropriate).

* > 6 mm in patients with gallbladder in situ or > 10 mm in patients after cholecystectomy.

EUS group (*n* = 50)

Diagnosis and treatment of bile duct stones. A total of 14 patients (28%, 95% CI 17–42) in the EUS group were shown to have bile duct stones. In one of them stones coexisted with an ampullary tumor. Stones were single in 11 cases, multiple in three cases, and had a median size of 10.5 mm (IQR 6–15mm). The diagnosis was established on initial EUS in 12 patients and during follow-up in two patients. In the latter, ERC with sphincterotomy was performed due to persistent symptoms 7 days after false-negative EUS, and revealed multiple stones of 1 mm in size. In addition, in one of these patients an ampullary adenocarcinoma was detected by biopsy taken from the papilla. Endoscopic removal of stones was successful in 12 patients, and failed in two patients. Because the latter patients declined surgery and were left untreated, the confirmation of stones is lacking in these cases. EUS findings, however, were evident; therefore EUS diagnosis was considered true-positive in the analysis. The ampullary tumor was successfully removed surgically and staged as T1N0 on pathological examination.

Number of endoscopic procedures. A total of 71 endoscopic procedures (mean per patient 1.42 ± 0.76) were performed in the EUS group in order to exclude, or detect and remove stones. This number included 52 EUS and 19 ERC procedures (Table 2).

Negative outcomes: complications of endoscopic procedures. Four patients (8%) suffered a total of six complications (Table 3); all were related to ERC with (*n* = 4) or (*n* = 2) without sphincterotomy.

Negative outcomes related to false-negative diagnosis of stones. Except for the detection of bile duct stones overlooked at initial examination in two patients described above, no negative outcomes were observed during the 1-year follow-up (Table 4).

Table 2 Number and type of endoscopic procedures performed to diagnose and treat bile duct stones

Type of endoscopic procedure	EUS group n = 50		ERC group n = 48	
	EUS	ERC	EUS	ERC
Successful initial examination	49	n. a.	n. a.	36
Unsuccessful initial examination	1	n. a.	n. a.	12
Second procedure after failed/ equivocal initial examination	0	0	6	7
Second procedure due to findings on initial examination (bile duct stones or ampullary tumor suspicion)	0	15	0	0
Repeated examination due to persistent symptoms during 1-year follow-up	2	4	2	0
Subtotal	52	19*	8	55 †
Total	71		63	

n. a., not applicable.

Data are numbers of endoscopic procedures.

* Including ERC with sphincterotomy in 14 patients.

† Including ERC with sphincterotomy in 14 patients.

Table 3 Complications of endoscopic procedures

Complications (incidence, type, and severity)	EUS group* n = 50	ERC group* n = 48
Patients with complications, n (%)	4 (8%)	19 (40%)
Number of complications	6	20
Complication type, n		
Acute pancreatitis	1	5
Transient abdominal pain	2	13
Delayed bleeding	2	0
Other †	1	2
Complication severity ‡, n		
Minimal-to-mild	3	15
Moderate	3	4
Severe	0	1
Fatal	0	0

* All complications were related to ERC with or without sphincterotomy.

† Rotator cuff tendinitis in the EUS group; transient post-ERC jaundice, tetany due to hyperventilation in the ERC group.

‡ Severity graded according to consensus criteria [17, 18].

Table 4 Events recorded during 1-year follow-up of patients initially diagnosed as having no bile duct stones or tumors

Type of event	EUS group n = 38*	ERC group n = 36
Patient lost to follow-up, n (%)	3 (8%)	3 (8%)
Events possibly or definitely related to overlooked bile duct stones, n (%)		
Repeated endoscopic examination of the bile duct resulting in diagnosis of stones	2 (5%)	0 (0%)
Hospitalization due to acute pancreatitis, acute cholangitis, or obstructive jaundice	0 (0%)	1 (3%) †

* 37 patients without stones on EUS and one patient in whom EUS was unsuccessful.

† Possibly related to, but without definite confirmation of bile duct stones.

ERC group (n = 48)

Diagnosis and treatment of bile duct stones. A total of 12 patients (25%, 95% CI 15–39%) in the ERC group were shown to have significant bile duct pathology, that is bile duct stones (n = 11), or an adenocarcinoma of the distal bile duct (n = 1). Stones were single in six and multiple in five cases, and had a median size of 8 mm (IQR 5–10 mm). They were detected and removed endoscopically in all cases. The tumor was detected on EUS that was carried out after failure of initial ERC, and was confirmed by biopsy and treated with stenting on subsequent ERC.

Number of endoscopic procedures. A total of 63 endoscopic procedures (mean per patient 1.31 ± 0.55) were performed in the ERC group in order to exclude or detect and treat stones. This number included 55 ERC and eight EUS procedures (Table 2).

Negative outcomes: complications of endoscopic procedures. Nineteen patients (40%) suffered a total of 20 complications of endoscopic procedures (Table 3); all these were related to ERC with (n = 6) or without (n = 14) sphincterotomy.

Negative outcomes related to false-negative diagnosis of stones. During the 1-year follow-up, one patient suffered an attack of acute pancreatitis, which was managed medically at another hospital. Although there was no definite confirmation of biliary etiology in this patient (no ERC/EUS was performed during or after pancreatitis), the event met the criteria for a negative outcome and was recorded as such (Table 4).

Comparison of EUS- and ERC-based management strategies

Table 5 summarizes the study results. In the EUS group, five patients experienced a total of eight negative outcomes, including six complications of endoscopic procedures and two false-negative diagnoses of stones. In the ERC group, a total of 21 negative outcomes occurred in 19 patients, including 20 complications of endoscopic procedures and one negative outcome possibly related to false-negative diagnosis of stones. The proportion of patients who had a negative outcome was significantly lower

Table 5 Summary of results

Study results	EUS group n = 50	ERC group n = 48	P value*
Patients with a negative outcome †, n (%)	5 (10%) ‡	19 (40%) §	< 0.001
95% CI	4–22	27–54	
Patients with bile duct stones or tumors, n (%)	14 (28%) ¶	12 (25%) #	> 0.05
95% CI	17–42	15–39	
Endoscopic procedures			
Total, n	71	63	> 0.05
Per patient, mean (SD)	1.42 (0.76)	1.31 (0.55)	
Per patient, median (IQR)	1 (1–2)	1 (1–2)	

CI, confidence interval; SD, standard deviation; IQR, interquartile range.

* Fisher exact test or Mann–Whitney U test as appropriate.

† Including complications of endoscopic procedures and negative outcomes possibly or definitely related to bile duct stones overlooked at initial examination.

‡ Eight negative outcomes in five patients.

§ 21 negative outcomes in 19 patients.

| No difference was observed when only moderate-to-severe complications were analyzed.

¶ In one patient stones coexisted with an ampullary tumor.

11 patients with stones and one with bile duct tumor.

in the EUS group than in the ERC group (10%, 95% CI 4–22%, versus 40%, 95% CI 27–54%; $P < 0.001$). This difference was mainly due to an excess of minimal-to-mild complications in the ERC group; no difference was observed when only moderate-to-severe complications were analyzed (6%, 95% CI 1–17, and 10%, 95% CI, 4–23, respectively). There were no significant differences between groups in the prevalence of bile duct stones or tumors, and in the number of endoscopic procedures performed.

Discussion

This is the first known randomized study to compare EUS- and ERC-based strategies in the management of bile duct stones. Previous, nonrandomized studies have focused on the diagnostic performance of the methods compared, rather than on their impact on the safety and efficacy of the bile duct stones management as a whole. Consequently, the net result of replacing ERC by EUS, although unanimously assumed to be beneficial, remained unproven.

The work presented here shows that when EUS was used to stratify patients into those who are stone-free and need no further testing, and those who have stones and need ERC for treatment, the management of bile duct stones was safer than the strategy based on ERC alone. In the EUS-based strategy, patients with stones required two separate procedures (EUS followed by ERC plus sphincterotomy) instead of only one (ERC plus sphincterotomy). This was offset, however, by the fact that EUS was successful in almost all patients in whom it was attempted. In contrast, initial ERC failed in 12 cases, which led to repeat examinations. As a result, the total number of endoscopic procedures needed to diagnose and treat stones was similar for both strategies. Also, the proportion of patients shown to have bile duct stones was similar in both groups, indicating that the compared strategies were equally effective in stone detection.

All complications were ERC-related, and not surprisingly, their number was in proportion to the number of procedures performed in each group. The 55 ERC procedures in the ERC group, and 19 ERC procedures in the EUS group (including 14 therapeutic ERC in each group) resulted in 20 and six complications, respectively.

The most frequent complication was transient abdominal pain, that started a few hours after the procedure, was usually associated with elevated serum amylase levels, and subsided within 24 hours, hence not fulfilling the criteria for a diagnosis of acute pancreatitis [17]. Such events are believed to represent a form of pancreatic reaction that does not eventually progress to genuine pancreatitis and has no serious consequences [21]. Although large multicenter studies that are evaluating the safety profile of ERC do not usually list transient pain under complications [22–24], these events evidently cause distress in patients and should not be ignored. In addition, they mimic initial symptoms of genuine pancreatitis, and for that reason alert medical personnel, lead to dietary restrictions, unnecessary testing, hospital admission or prolongation of hospital stay.

There is also evidence to suggest that transient post-ERC pain is not uncommon. In placebo-controlled, randomized trials evaluating the pharmacological prevention of pancreatic injury by means of drugs such as gabexate, somatostatin, or octreotide, and strongly focused on ERC complications, pain was reported to occur in 22.5% of patients on average (median of results of 10 trials; data for placebo arms) [25]. The frequency of this compli-

cation in the patients in this study was similarly high (20%). This may be due to selection of patients with intermediate probability of stones, resulting in a high proportion of young to middle-aged patients, females, and individuals with a nondilated bile duct and normal bilirubin level (Table 1). Although the prevalence of sphincter of Oddi dysfunction in the current group is not known, it may also have been high. All these characteristics have been shown to be risk factors for post-ERC pancreatitis [22–24,26,27], and may explain the high rate of transient pain. Another explanation may be the fact that data on complications were collected prospectively on an in-hospital basis. This may have resulted in the inclusion of some events that otherwise would have gone unnoticed. However, it should be emphasized that only clinically significant events that required parenteral administration of analgesic/antispasmodic drugs were recorded. The frequency of genuine pancreatitis in the patients in the current study was within the typical range (8%, or six events after a total of 74 procedures in both groups) [14,23,24,27].

Although the explanation for the high frequency of transient pain remains speculative, it was this complication that accounted for the major part of morbidity in the ERC group, and for the significant difference in morbidity between groups (Tables 3 and 5). The number of moderate and severe complications was low and similar in both groups, as was the number of negative outcomes related to stones overlooked at initial examination (defined as either detection of overlooked stones, or occurrence of complications during follow-up that were possibly related to overlooked stones). Such late events occurred in only three patients (two in the EUS and one in the ERC group).

Two of 38 patients (5%) found to be stone-free at the initial EUS were eventually found to have stones during follow-up. For both patients, the reasons for performing ERC were persistent biliary symptoms, and there was only a short delay between the false-negative EUS and the subsequent ERC (7 days in both cases). Similar results have been reported in three other studies focusing on the follow-up of patients in whom bile duct stones were excluded by means of EUS: stones were detected subsequently in a small proportion of cases (1% to 6%), and as a rule within a few weeks after false-negative EUS [11,12,28]. This indicates that in patients who are found to be stone-free at initial EUS but continue to have biliary pain episodes, the decision to perform ERC should not be deferred. Sphincterotomy followed by instrumental revision should be considered in such cases because stones overlooked by EUS tend to be very small, and are likely to also be missed on a cholangiogram. This was the case in two patients discussed here, as well as in the previous experience of our group and others [4,9,10].

Of concern is the fact that a small ampullary cancer (T1N0 on subsequent pathologic examination) that coexisted with tiny stones in one of the patients discussed above was overlooked. The papilla in this patient appeared normal both endoscopically and endosonographically, and the only abnormality found on EUS and ERC was moderate bile duct dilatation. The dilatation (along with clinical symptoms and recurrent biliary pain) prompted the endoscopist to perform sphincterotomy and obtain a biopsy, which eventually led to the diagnosis of cancer and stones. This case indicates that patients with dilated ducts should be treated with caution.

It should be noted that the results discussed above were achieved in a patient population with a bile duct stones prevalence of 25%–28% (26.5% for the whole study group). If this figure had been higher or lower, the number of endoscopic proce-

Limitation	Interpretation
The primary end point was a composite of adverse events of various types and severity	Difference between groups was mainly due to an excess of minimal to mild complications in the ERC group. No difference was observed when only moderate to severe complications were analyzed*
An open trial; investigators who assessed the negative outcomes were not blinded to group assignment	Assessment bias with potential impact on primary end point cannot be excluded*
High ERC failure rate	Repeated procedures increased the total number of procedures in the ERC group. Possible bias in favor of EUS
Relatively low case volume per year	Potential impact on the complication rate and number of failed procedures
Patients who had bile duct stones removed were not followed up. Late complications might have been missed	Because proportion of patients with stones was similar in both groups, bias is unlikely
Follow-up limited to one year. Late manifestations of overlooked stones might have been missed	Possible but unlikely impact on the primary end point
The decision to repeat ERC or EUS during follow-up was at the discretion of physician directly caring for the patient (no pre-specified criteria)	It cannot be excluded that patients in the EUS group were more likely to be re-tested during follow-up because the results of EUS were considered less trustworthy. Bias against EUS possible, yet unlikely
The majority of included patients had already had a cholecystectomy	Limited generalizability of the results to patients with gallbladder in situ

* For more details, see Discussion.

Table 6 Limitations of the study

dures and complication rates might have also been different (the prevalence of bile duct stones in the treated group determines the demand for ERC and sphincterotomy in the EUS-based strategy, and hence, the number of endoscopic procedures and complication rate). This emphasizes the role of the model used to assess the pre-test probability of bile duct stones and select patients for the study. The model proposed by Barkun et al. [15,16] was chosen here for three reasons: (i) it involves only simple and objective parameters (age, bilirubin level, and data from transabdominal ultrasound); (ii) it provides a numeric value for the probability of bile duct stones; and (iii) most importantly, it has been validated in a prospective study [15]. Despite the fact that it was originally developed for patients with gallbladder stones scheduled for laparoscopic cholecystectomy, it proved to be useful in the study group presented here, that included mainly patients after a cholecystectomy. The arbitrarily chosen upper limit for probability of bile duct stones, i.e. 67%, resulted in the appropriate selection of patients; consequently, the actual prevalence of bile duct stones, of 26.5%, was in the range defined as intermediate (10%–55%) and recognized as representing, for economic and medical reasons, an ideal target for an EUS-based strategy [13].

An important limitation of the study was that the endoscopists performing ERC knew that they were dealing with a special group of patients, characterized by a rather high risk of complications and a probability of stones that was moderate at most. Furthermore, EUS was available as a back-up procedure in case of ERC failure. Under such circumstances, the determination to achieve cannulation could have been weakened, and this may explain the fact that initial ERC failed in 25% of patients in the ERC group. Most probably, in many of these cases, prolonged efforts at cannulation would have resulted in a successful ERC had the endoscopist not decided to discontinue the procedure early in order to avoid risk. (As shown in a large, multicenter study,

in 14% of patients more than 15 attempts on the papilla are needed before cannulation is finally achieved; on the other hand, difficult cannulation is a known risk factor for pancreatitis [23]). Also, aggressive techniques such as precut papillotomy were not used for safety reasons. Failure to opacify the bile duct led to repeated examinations, inflating the number of endoscopic procedures in the ERC group. As a result, the secondary end point of the study may have been affected.

Another limitation is that investigators who assessed the negative outcomes were not blinded to group assignment. Although assessment bias from that source cannot be excluded, it was rather unlikely; for any event to be recorded as a negative outcome, it had to meet strict, predefined criteria. Other limitations of the study, and their potential impact on the results, are summarized in [Table 6](#).

Conclusions

This randomized study confirmed that diagnostic ERC should be replaced by EUS in the management of patients with intermediate probability of bile duct stones. EUS, followed by ERC performed selectively in patients with confirmed stones, was a safer management strategy than that based on ERC alone. The number of endoscopic procedures needed to diagnose and treat stones was found to be similar for EUS- and ERC-based strategies.

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Competing interests: None

Risk factors for bile duct stones				Probability of bile duct stones
Age > 55 years	Bilirubin level: > 30 $\mu\text{mol/L}$	CBD dilatation on ultrasound*	Bile duct stones on abdominal ultrasound	
+	+	+	+	94%
+	+	+	(-)	72%
+	+	(-)	+	85%
+	+	(-)	(-)	50%†
+	(-)	+	+	90%
+	(-)	+	(-)	61%†
+	(-)	(-)	+	> 67%
+	(-)	(-)	(-)	38%†
(-)	+	+	+	85%
(-)	+	+	(-)	49%†
(-)	+	(-)	+	69%
(-)	+	(-)	(-)	28%†
(-)	(-)	+	+	> 67%
(-)	(-)	+	(-)	38%†
(-)	(-)	(-)	+	58%†
(-)	(-)	(-)	(-)	19%†

CBD, common bile duct.

* > 6 mm in patients with gallbladder in situ or > 10 mm in patients after cholecystectomy.

† Patients with probability of bile duct stones of no more than 67% were admitted into the study.

Table A1 Model for determining baseline probability of bile duct stones in patients screened for eligibility criteria [15, 16]

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Correction

Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy* 2005; 37: 960–965

Abstract, Results (p. 960)

A total of 1349 instances of disease were identified in the 530 examinations. Capsule endoscopy solely detected 87% of the disease instances, while the comparison method solely detected 13%. The yield for push enteroscopy alone was 14.8%, for small-bowel series it was 9.9% and for colonoscopy it was 13.2%. Capsule endoscopy missed 146 disease instances for a miss rate of 10%; 989 were missed by the comparison methods for a miss rate of 73%; and 214 were detected by both methods.

This should read: A total of 1349 instances of disease were identified in the 530 examinations. Capsule endoscopy solely detected **73%** of the disease instances, while the comparison method solely detected **11%**. The yield for push enteroscopy alone was 14.8%, for small-bowel series it was 9.9%, and for colonoscopy it was 13.2%. Capsule endoscopy missed 146 disease instances for a miss rate of **11%**; 989 were missed by the comparison methods for a miss rate of 73%; and 214 were detected by both methods.

The first paragraph of the discussion (p. 963/964):

Capsule endoscopy has revolutionized the endoscopic examination of the small bowel. The data presented here have shown capsule endoscopy to have a significantly greater detection capability for suspected disease of the small intestine compared with push enteroscopy, small-bowel series and colonoscopy with ileal intubation. Capsule endoscopy identified disease in approximately 70% of the examinations, double the yield of other methods. Approximately 90% of 1349 instances of disease were not identified by any other method other than capsule endoscopy.

This should read: Capsule endoscopy has revolutionized the endoscopic examination of the small bowel. The data presented here have shown capsule endoscopy to have a significantly greater detection capability for suspected disease of the small intestine compared with push enteroscopy, small-bowel series and colonoscopy with ileal intubation. Capsule endoscopy identified disease in approximately 89% of the examinations, whereas 27% were detected by the comparison

method. **Approximately 73% of 1349 instances of disease were not identified by any other method other than capsule endoscopy.**

The second paragraph on p. 965:

Similar results were encountered for the non-bleeding studies. In these studies, 52.8% of patients had findings not identified by any other method and the overall rate of findings was 70%. This compares favorably with the comparison methods, which found 12.8% of lesions solely and had an overall yield of 31%.

This should read: Similar results were encountered for the non-bleeding studies. In these studies, 52.8% of patients had findings not identified by any other method and the overall rate of findings was **70% for capsule endoscopy**. This compares favorably with the comparison methods, which found **11.8%** of lesions solely and had an overall yield of **35.4%**.

Table 4, column “none”, line “nonbleeding” (p. 963):

37 cases, 12.8%.

This column should read: 37 cases, 11.8%.

The last paragraph (p. 965):

In summary, this pooled analysis shows capsule endoscopy to be the state-of-the-art tool for small-bowel imaging. It is superior to push enteroscopy, small-bowel series, and colonoscopy with ileal intubation. The yield of capsule endoscopy for identification of disease is double the yield of the other methods, and when observations of disease are counted individually, 90% of instances cannot be seen by any other method.

This should read: In summary, this pooled analysis shows capsule endoscopy to be the state-of-the-art tool for small-bowel imaging. It is superior to push enteroscopy, small-bowel series, and colonoscopy with ileal intubation. The yield of capsule endoscopy for identification of disease is double the yield of the other methods, and when observations of disease are counted individually, **73%** of instances cannot be seen by any other method.