Author's response to reviews

**Title:** Linear Echoendoscope-Guided ERCP for the Diagnosis of Occult Common Bile Duct Stones

**Authors:**

Hoi-Hung Chan (hoihungchan@gmail.com)
E-Ming Wang (emwang@vghks.gov.tw)
Meng-Shun Sun (dtmed655@yahoo.com.tw)
Ping-I Hsu (williamhsup@yahoo.com.tw)
Wei-Lun Tsai (wltsai@vghks.gov.tw)
Wen-Chi Chen (wcchen@vghks.gov.tw)
Tzung-Jiun Tsai (tjtisai@vghks.gov.tw)
Kai-Ming Wang (kmwang@vghks.gov.tw)
Huei-Lung Liang (hlliang@vghks.gov.tw)
Kwok-Hung Lai (khlai@vghks.gov.tw)
William Robert Brugge (wbrugge@partners.org)

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**Author's response to reviews:** see over
Dear Editor,

Attached is a revised copy of the paper entitled “Linear echoendoscope-guided ERCP for the diagnosis of occult common bile duct stones” by Hoi-Hung Chan, et al. We would like to submit this article for publication as an original article in your outstanding journal.

The current study included thirty patients with biliary colic, pancreatitis, unexplained derangement of liver function tests, and/or dilated CBD for testing the role of linear EUS in identifying an occult CBD stones.

When a CBD stone was disclosed by linear EUS, ERCP with stone extraction was performed. Patients who failed ERCP were referred for surgical intervention. If no stone was found by EUS, ERCP would not be performed and patients were followed-up for possible biliary symptoms for up to three months. Of the 12 patients
who were positive for CBD stones by EUS, nine had successful ERCP, one failed ERCP (but was later treated successfully by surgical intervention) and two were false-positive cases. No procedure-related adverse events were noted. For those 18 patients without evidence of CBD stones by EUS, no false-negative case was noted during the three-month follow-up period. Linear EUS had sensitivity, specificity, positive and negative predicted values for the detection of CBD stones of 1, 0.9, 0.8 and 1, respectively. We conclude that linear EUS is safe and efficacious for the diagnosis of occult CBD stones in patients with intermediate risk for the disease. We hope that our findings can be helpful for clinical practice.

The listed Authors would like to express that 1) all participated actively in the study; 2) all have read and approved the submitted manuscript; 3) the study complies with current ethical considerations; 4) the manuscript reports an unpublished work which is not currently under consideration elsewhere and will not be submitted to another journal until a final decision has been made; and 5) there are no conflicts of interest, unless those identified specifically by the Authors in the letter.
Point-by-point response to the concerns

A. Dear Dr. Werner Hartwig (Referee 1),

(Major Compulsory revisions)

1. As it has been demonstrated by several studies before, EUS is well established in several centers in the evaluation of patients with suspected bile duct stones. This is true for radial (several randomized studies that compared EUS with ERCP for detection of CBD stones) as well as linear EUS (e.g., Kohut et al, World J Gastroenterol 2003 or Endoscopy 2002). It is unclear to the reviewer: what are the new findings of the study? Please discuss.

Thank you for providing excellent papers for references.

It is true that there was no new finding in our study. However, there were only two reports about the efficacy of linear EUS in the evaluation of patients with suspected bile duct stones well written by the same author, Dr. Kohut, which clearly not sufficient when considering about the quantity of papers. Moreover, one of them only focuses on patients with high suspicion for CBD stones. We do further emphasize that a considerable portion of patients with intermediate risk of CBD stones was found to have no evidence of stones by linear EUS, whom can avoid unnecessary invasive evaluation of the bile duct with ERCP.
2. There is no “gold standard” for the detection of CBD stones in the study. Since ERCP has been only performed in EUS CBD-stone positive patients and follow-up of patients has, in part, been conducted by telephone only, the rate of false negative findings may be underestimated. Another shortcoming of the study is that EUS and ERCP have been performed by the same investigator and no blinding has been performed. The authors should include a paragraph in the discussion where the shortcomings of the study are detailed.

Thank you for giving a very important comment that is worth discussing in more detail. We have added a related paragraph in the discussion.

3. Diagnostic studies should also provide data about positive and negative predicted values.

Please provide data.

Thank you for your reminder! We have added the positive and negative predicted values into the text (Positive and negative predicted values for the detection of CBD stones were 0.8 and 1 respectively).

4. In the discussion, the authors tend to neglect possible disadvantages of EUS, e.g., the invasiveness of EUS compared to MRCP. Why do the authors think that MRCP needs more manpower as compared to invasive EUS?
Thank you so much for your question! We have added the character of “invasiveness of EUS” and deleted the term “extensive manpower” for MRCP in the text.

5. No abstract has been available to the reviewer. Please provide.

We apologize for the inconvenience and will certainly provide!
B. Dear Dr. Hjalmar van Santvoort (Referee 2),

Major Compulsory Revisions:

INTRODUCTION:

1. The current aim of the study as formulated at the end of the introduction is misleading; please delete “as an alternative to both MRCP and radial EUS” as this was not a comparative study. Moreover, “the potential” is rather vague. I would rephrase the introduction to state clearly the goal of the study, which in my opinion was: “The aim of this study was to investigate the safety and diagnostic accuracy of linear EUS in detecting occult CBD stones”.

Thank you for your valuable suggestions! We have deleted “as an alternative to both MRCP and radial EUS” and added the sentence “the aim of this study was to investigate the safety and diagnostic accuracy of linear EUS in detecting occult CBD stones” in the INTRODUCTION.

METHODS:

2. The inclusion criteria are not clear: What if CBD stones were seen on conventional US; were these patients included in the current study? Moreover, in the aim of the study, it is stated that patients with “intermediate risk for CBD stones” are studied; how was “intermediate” defined in the eligibility criteria?

No, patients with CBD stones seen on conventional US were not included in the
current study. The probability of CBD stones was determined according to the criteria proposed by Barkun et al. (Useful predictors of bile duct stones in patients undergoing laparoscopic cholecystectomy: McGill Gallstone Treatment Group. Ann Surg 1994;220:32-9.)

Patients with an intermediate risk for CBD stone were evaluated for the study, which means that the baseline probability of bile duct stones is no more than 67%.

3. An exclusion criterion was the presence of CBD stones on conventional US/CT scan. Hence, the patient population of this study is highly selected and the results of this study cannot be extrapolated to all patients with clinical or biochemical suspicion of CBD stones. This is not a problem, as long as the authors clearly state that the study focused only on patients where conventional imaging failed to identify CBD stones. In this respect, it should be reported in the results section whether all 30 patients underwent transabdominal US and/or CT before they were included in the study. The issue should also be emphasized in the discussion section.

Thank you for giving a very important comment that is worth discussing in more detail.

No direct evidence of CBD stone was found by transabdominal ultrasound (30 patients) and CT scan (24 patients, others did not receive CT scan exam).
4. From a methodological point of view, the diagnostic test in this study was linear EUS. The gold standard was ERCP. However, the gold standard was not performed in all patients; if EUS was negative, patients did not receive ERCP. This may have led to a false negative result, underestimating the diagnostic accuracy of EUS. The issue should be addressed in the discussion section as a major shortcoming.

Thank you for your reminder! The issue has been addressed in the discussion section as a major shortcoming.

RESULTS:

5. In 15 patients, the reason for inclusion was acute pancreatitis. This was, however, not defined as an inclusion criterion in the methods section. Were there other signs of CBD stones in the patients? Were there other plausible causes for pancreatitis in these patients, as it may be an overkill in diagnosis to perform EUS in every patient with acute pancreatitis

Thank you so much for your reminder!

In addition to pancreatitis, these 15 patients presented with at least one or more of the following signs of CBD stones, which include: jaundice (eight patients), dilated CBD (five patients), GB stones (nine patients) and elevated Alkaline-phosphatase and Gamma-glutamyltransferase (ten patients).
DISCUSSION

6. As previously stated, the fact that the study population represents a subgroup of patients with suspicion of CBD stones, and that ERCP was not performed as the gold standard in all patients, should be addressed in the discussion. This also means that the conclusion is currently much too strong. Please state in the conclusion only something like “This study suggests that linear EUS can accurately detect CBD stones in patients where conventional imaging techniques have failed”

Thank you so much for your advice! We have added the following paragraph in the discussion:

In addition, there is no “gold standard” for the detection of CBD stones in the study. Since ERCP has been only performed in patients with positive CBD stone by EUS and follow-up of patients has in parts been done by telephone only, the rate of false negative findings may be underestimated.

We also changed the conclusion to “This study suggests that linear EUS can accurately detect CBD stones in patients with intermediate risk for the disease, when conventional imaging techniques have failed.”.
Minor Essential Revisions

INTRODUCTION

7. The introduction could be shortened, for instance, by moving background information on linear EUS to the discussion section.

Thank you for your reminder! We have removed the following paragraph from the background to the discussion section.

One should also notice that the learning curve of linear EUS is steep; therefore, its efficacy is highly operator dependent. It is also not readily available in most clinical settings. However, the images obtained by linear EUS are similar to that of the ordinary transabdominal ultrasound, and, due to the close proximity of the ultrasound probe to the CBD, any intraductal lesions (including tumor) can be readily observed.

METHODS

8. In the last paragraph of the methods section (page 9, line 15) the study design is clearly stated. Move this information to the beginning of the methods section.

Sure!

9. The authors provide a rationale for the sample size of 30 patients? If this was arbitrarily chosen, please also state this.

Yes, this was arbitrarily chosen. We have added the term to the method.
RESULTS

10. Of the 12 patients with positive EUS, 2 patients “were false-positive cases”. Why were these false-positives? Did these patients undergo ERCP, and if so, was ERCP performed immediately following EUS? If not, the CBD stones may have migrated before ERCP was performed.

Thank you for giving a very important comment that is worth discussing in more detail.

Of the 12 patients who were positive for CBD stones by EUS, eight of them were treated successfully using ERCP in the same session. One patient, who had failed in the same session of EUS, was treated successfully by ERCP 32 days later due to refusal of surgery by patient. Another one failed ERCP was later treated successfully by surgical extraction. There were two false-positive cases. In one, no gross stone was extracted during ERCP procedure, and no stone crystal was found in the aspirated bile under the microscopic exam. Therapeutic ERCP failed for the other case and the absence of a stone was proved by surgery.
11. Please add an abstract to the manuscript

   Sure!

12. Although the paper is generally well written, there is still some room for improving grammar and style; e.g., (page 4, line 7) do not use past tense “stones were 77.3%..” but “stones are”; and (page 4, line 10) do not use “has been the gold standard” but “is the gold standard”.

   Thank you for your reminder! We have improved the style.

13. Please use decimals when presenting percentages; e.g., 15% instead of 15.1%

   Thank you so much for your advice! We have made the changes accordingly.
C. Dear Dr. Martin Freeman (Referee 3),

Minor points

In the Introduction, it has been shown that the rate of post-ERCP pancreatitis may be as high as 15.1%, which includes 1% of patients graded as severe in degree.[9] (THIS IS IN HIGH RISK PATIENTS WITH SUSPECTED SPHINCTER OF ODDI DYSFUNCTION, NOT BILE DUCT STONES. SHOULD ADD A STATEMENT TO THAT EFFECT.

Moreover, the diagnostic rate is dramatically reduced for smaller CBD stones (#5 mm). [13] PLEASE STATE THE RATE.

Thank you for giving two very important comments! We have made the corrections.

In the Methods section, need to state "GOLD STANDARD" for TRUTH STANDARD for definition of bile duct stone. What was considered true positive, true negative, false positive and false negative? Was ERCP truth standard? If so what? Please calculate positive and negative predictive values in addition to sensitivity and specificity

Is this appropriate? Stones seen at EUS can easily be missed by cholangiography and even balloon extraction.

Otherwise, a worthwhile paper.
There is no “gold standard” for the detection of CBD stones in the study. Since ERCP has been only performed in patients with positive CBD stone by EUS and follow-up of patients has in parts been done by telephone only, the rate of false negative findings may be underestimated. Patients with stones correctly identified by EUS who were subsequently proved by ERCP or surgery are considered true positive. Patients who had no stones, but were incorrectly diagnosed by EUS and subsequently disclosed by ERCP (with bile analysis) or surgery were considered false positive. Patients who had no stones, but were correctly diagnosed by EUS and found to have no biliary symptoms during the follow-up period, were considered true negative. Patients who had stones in their bile ducts, but were missed by EUS and finally found to be symptomatic during the period of follow-up, were considered false negative.

Looking forward to hearing from you soon.

Best regards!

Sincerely yours,

Hoi-Hung Chan, MD, PhD