—Review Article—

The incremental benefit of EUS for the identification of malignancy in indeterminate extrahepatic biliary strictures: A systematic review and meta-analysis

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ABSTRACT

This systematic review aims to assess the literature to determine the impact of EUS for diagnosing malignancy among indeterminate extrahepatic biliary strictures. A systematic review was performed using MEDLINE, EMBASE, Cochrane, and conference proceedings from inception to July 2016. Pooled results were calculated using random-effects model, and heterogeneity was explored using stratified meta-analysis and meta-regression. The main outcome was the incremental benefit of EUS (IB_{EUS}) for the diagnosis of malignancy among patients who have undergone ERCP with brushing cytology for extrahepatic biliary strictures. Of 3131 identified citations, ten met the inclusion criteria and were included in the final analyses (study periods from 1998 to 2014). Pooled IB_{EUS} estimate with the adjustment for publication bias was 14% (95% confidence interval, 7%–20%). Individual studies demonstrate that the IB_{EUS} is greater for distal biliary strictures or when an extrinsic mass is identified on cross-sectional imaging. EUS increases the identification of malignancy for indeterminate biliary strictures following a nondiagnostic ERCP, particularly those that are distal or related to extrinsic compression.

Key words: Diagnosis, ERCP, biliary stricture, EUS, EUS-FNA, incremental benefit, malignancy

INTRODUCTION

It is challenging to differentiate between benign and malignant causes of biliary strictures. Currently, ERCP with brush cytology is the primary investigative modality, enabling diagnosis, and therapeutic benefit with stricture dilation and stent placement.[1] However, as the sensitivity of ERCP brushings is 45%, a large proportion of biliary strictures would remain indeterminate using this approach alone.[2]

EUS with fine-needle aspiration is a highly accurate tool for this purpose, with a sensitivity and specificity of 80% and 97%, respectively.[3] Some studies have shown

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increased diagnostic yield for malignancy with EUS following nondiagnostic ERCP;[4,5] however, they vary in design, patient population, and results. To determine the added utility of EUS in diagnosing malignant strictures, it must be examined in the context of current practice protocols for extrahepatic biliary strictures and account for the fact that ERCP will diagnose some cases without the need for EUS. Therefore, this systematic review with meta-analysis aims to review the literature to investigate the incremental benefit of EUS (IB_{EUS}) following a nondiagnostic ERCP with brushing cytology for diagnosing malignancy in adult patients presenting with extrahepatic biliary strictures.

METHODS

This systematic review was prospectively registered on the PROSPERO international database, registration number CRD42016043987.[6] It is also reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7]

Search strategy

With the support of an expert medical science librarian, the investigators created a bibliographic database search strategy to determine the use of EUS following ERCP with brushing cytology in patients with extrahepatic biliary strictures. Three major search themes were created. The first theme, *malignant extrahepatic biliary stricture*, combined the Medical Subject Headings (MeSH) terms such as *bile duct disease*, *biliary tract neoplasm, gallbladder neoplasms*, *cholangiocarcinoma*, *cholangiocellular carcinoma*, *biliary atresia*, *biliary obstruction*, *biliary stricture, extrahepatic bile duct*, and *cholestasis*. The second theme, *endoscopic retrograde cholangiopancreatography*, combined the MeSH terms such as *endoscopic retrograde cholangiopancreatography*, *ERCP*, and *endoscopic cholangiopancreatography*. The third theme, *endoscopic ultrasound*, combined the MeSH terms such as *endosonography*, *endoscopic ultrasound*, *interventional ultrasonography*, *endoscopic ultrasound-guided fine-needle aspiration*, and *biopsy*. All three major search themes with corresponding MeSH terms were subsequently combined using the Boolean operator "AND" [Supplementary Table 1].

A medical librarian then utilized the above search strategy to identify the articles in MEDLINE, EMBASE, Cochrane, and conference proceedings from inception to July 2016. Database searches were supplemented by screening the reference lists of relevant studies.

Study selection

Two reviewers independently reviewed the titles and abstracts to identify the articles for full-text review. Any discrepancies in the inclusion of abstracts between reviewers were reconciled by a third reviewer. The same described method was used to perform a full-text review and select the final studies for data analysis. The following inclusion criteria were used: (1) patients were being evaluated for biliary strictures, (2) each patient underwent at least one ERCP, (3) EUS was performed following ERCP, (4) outcomes measured included diagnosis of malignancy, and (5) observational studies (prospective and retrospective) or randomized controlled trial studies. Studies were excluded if patients were younger than 18 years old, "if" initial study population already had a nondiagnostic ERCP or had insufficient data. Case reports or case series were also excluded. Articles published in all languages were considered.

Data extraction and study outcomes

The first two reviewers independently extracted the data from the final list of articles fulfilling the inclusion criteria using a standardized data collection form. Disagreements were reviewed, and consensus on selection was derived with the guidance of the third reviewer. Primary outcomes of interest were number of patients who received an ERCP for suspected biliary stricture, number of patients who had an EUS following an ERCP, and number of cases where EUS alone detected malignancy (ERCP did not yield a diagnosis of malignancy, but EUS did). These were used to calculate the IB_{EUS} as described below. Other data extracted included study information, study design, sample size, study population demographics, stricture location, whether ERCP and EUS were performed in tandem, and other imaging modalities utilized. Study authors were contacted for unpublished data and in instances of missing data.

The diagnosis of malignancy by EUS alone, following nondiagnostic ERCP, was measured by calculating the IB_{EUS}, which was expressed as $IB_{EUS} = (N_{EUS})/(T_{ERCP})$, where T_{ERCP} is the total number of patients who underwent ERCP with brushings for suspected malignant biliary strictures and N_{EUS} is the number of patients who underwent both an ERCP and EUS (following ERCP), where EUS alone identified malignancy. This formula has been described elsewhere to examine the impact of EUS[8] and highlights the additional diagnostic value of EUS in the context of

an existing diagnostic pathway for the investigation of biliary strictures.

Risk of bias

The first two reviewers evaluated the study quality of included studies using the Newcastle–Ottawa Quality Assessment Scale Criteria.[9] This included assessing for (1) description of cohort, (2) selection of controls, (3) report of ERCP as initial investigation, (4) description of patients who underwent EUS, (5) description of biliary stricture location, (6) notation of potential confounders, (7) report of the final diagnosis for all patients, (8) adequate follow-up of all patients, and (9) explanation for nondiagnostic outcomes.

Statistical analyses

The approach to statistical analyses as described in previous studies was used in this systematic review.[8]

IB_{EUS} and its variance were represented using the logit of proportion (lP).[8] For sample size proportional weighting, the standard error of each study was calculated.[8] The lP was summarized across studies using a random effects model and the methods proposed by DerSimonian and Laird.[8,10] The lP was then converted to the IB_{EUS} and the corresponding 95% confidence interval (CI).[8] Small-study effects and publication bias were evaluated through the visual inspection of funnel plots and Begg's asymmetry test.[8]

Heterogeneity of IB_{EUS} across studies was assessed via the inspection of asymmetry among forest plots and calculation of the I^2 inconsistency statistic.[8]

Meta-analyses and meta-regression of the study characteristics were performed to evaluate its effects on pooled estimates of effects. *A priori* characteristics included study origin, publication form, quality score, study design, use of other imaging modalities, use of tandem EUS and ERCP, and use of EUS for all patients.

RESULTS

The process of identifying articles for the systematic review is summarized in Figure 1. Among 3131 citations, nine studies met the inclusion criteria. After contacting the study authors of included abstracts, Kim *et al.* provided their recent publication in the full text.[11,12] This resulted in a total of ten studies included in the final analyses. The studies reported original data regarding the use of EUS following ERCP with brushing cytology in patients with extrahepatic biliary strictures. Inter-rater agreement for abstract and full-text review was 0.24 and 0.47, respectively.

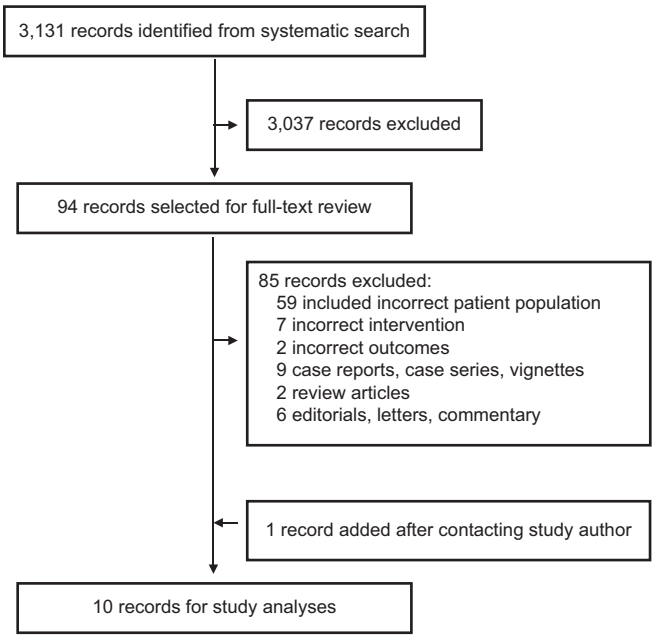

Figure 1. Flowchart illustration of study selection for meta-analysis

Study characteristics

The characteristics of the ten studies are shown in Table 1. Six were prospective studies and four were retrospective studies. All but one were single-center studies. The average age of the study participants was between 62 and 72 years. The total number of patients included in the studies ranged from 23 to 311, with a total of 1162 patients across all studies. Of these, 314 patients had an EUS following nondiagnostic ERCP. Of note, in three studies, ERCP and EUS were performed during the same session. In two studies, the use of EUS depended on the location of stricture.

Risk of bias assessment

The study quality and the corresponding summary score according to the Newcastle–Ottawa Scale for each of the ten studies are displayed in Table 2. The median quality score was 7 out of 9. Consecutive recruitment was described in four of the studies. In the three studies (as noted above) where ERCP and EUS were performed as paired procedures, it could not be ascertained of whether all patients had a nondiagnostic ERCP before undergoing EUS. However, the results of the first procedure were unavailable to the performers of the second procedure. Stricture location was noted in six of the studies, and possible confounders were noted in five.

Table 1. Characteristics of studies included for meta-analysis

Study	Study period	Country	Study design	Total number of patients	Average age (years)	Number of patients who had an ERCP	Number of patients who had EUS	Number of cases where EUS alone detected malignancy
Lee *et al.*, 2017[12]	2012-2014	South Korea	Prospective	202	69.4	190	33	26
Lee *et al.*, 2016[13]	Unknown	South Korea	Prospective	120	Unknown	120	19	18
Kim *et al.*, 2013[11]	Unknown	South Korea	Prospective	76	Unknown	76	17	15
Hijioka *et al.*, 2012[14]	2001-2010	Japan	Retrospective	83	64.8	59	19	19
Lo *et al.*, 2011[15]	Unknown	USA	Prospective	23	66	23	8	3
Ohshima *et al.*, 2011[16]	2007-2009	Japan	Retrospective	225	71.5	225	22	16
Fargahi *et al.*, 2010[17]	1998-2009	USA	Retrospective	311	Unknown	311	75	10
Oppong *et al.*, 2010*[18]	2004-2007	United Kingdom	Prospective	38	62.4	37	37	7
Saifuku *et al.*, 2010*[19]	2005-2008	Japan	Retrospective	34	71	34	34	17
Rösch *et al.*, 2004[20]	1998-2000	Germany	Prospective	50	62.1	50	50	7

*ERCP and EUS±FNA were performed during the same session

Table 2. Quality assessment of studies included in the meta-analysis

Study	Cohort described	Selection controls	Exposure ascertained	Malignancy identified	Stricture location noted	Stratification by other factors	Verification of malignancy	Adequate study length	Follow-up adequate	Quality Score
Lee *et al.*, 2017[12]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Lee *et al.*, 2016[13]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Kim *et al.*, 2013[11]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Hijioka *et al.*, 2012[14]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Lo *et al.*, 2011[15]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Ohshima *et al.*, 2011[16]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Fargahi *et al.*, 2010[17]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Oppong *et al.*, 2010[18]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Saifuku *et al.*, 2010[19]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Rösch *et al.*, 2004[20]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

Proportion of cases where EUS alone identified malignancy

The pooled IB_{EUS} was 15% (95% CI 9%–24%) [Figure 2]. There was no significant heterogeneity noted across studies (I^2 = 0%, P = 0.075). In the stratified analyses based on publication characteristics, the estimate of effect was not significantly influenced by whether EUS was performed on all patients or selectively, whether consecutive recruitment was used in the study, or whether a prospective or retrospective study design was used.

Studies that were published in full text, from Asia, and included computed tomography (CT) and/or magnetic resonance imaging (MRI) yielded higher estimates of effect. Furthermore, studies where ERCP and EUS were conducted in tandem observed greater estimates of effect as compared to when modalities are performed on separate occasions. The full details are shown in Table 3.

Assessment of evidence of publication bias

Visual inspection of the funnel plot showed asymmetry [Figure 3]. This was confirmed with a Begg's test of P = 0.01. Adjusting for small-study effects and publication bias using the "trim-and-fill method," the adjusted estimate was 13.6% (95% CI 6.7%–20.4%).

Table 3. Stratified analysis of pooled incremental benefit of EUS in identifying malignancy after nondiagnostic ERCP

Characteristic	Stratified analysis		Meta-regression		
	Number of studies	Pooled proportion (IBEUS)	Heterogeneity I^2 statistics (%)	τ^2 statistics	*P*
Publication type					
Abstract	4	0.10 (0.05-0.21)	18.2	<0.01	0.37
Full text	6	0.19 (0.11-0.32)			0.01
Study type					
Prospective	6	0.15 (0.12-0.19)	21.8	<0.01	0.61
Retrospective	4	0.15 (0.05-0.41)			0.05
Study location					
Asian country	6	0.19 (0.11-0.32)	8.7	<0.01	0.20
Non-Asian country	4	0.09 (0.04-0.19)			0.24
Recruitment method					
Consecutive	4	0.15 (0.12-0.19)	25.2	<0.01	0.83
Nonconsecutive	6	0.16 (0.07-0.31)			0.02
Use of CT scan					
Yes	2	0.19 (0.15-0.25)	17.7	<0.01	0.35
No	8	0.13 (0.08-0.20)			0.02
Use of MRI					
Yes	3	0.18 (0.06-0.43)	27.3	<0.01	0.90
No	7	0.14 (0.08-0.23)			0.02
Tandem ERCP and EUS					
Yes	3	0.25 (0.12-0.46)	7.5	<0.01	0.18
No	7	0.12 (0.07-0.20)			0.01
EUS for all patients					
Yes	4	0.15 (0.05-0.38)	24.0	<0.01	0.77
No	6	0.15 (0.10-0.22)			0.01
Study quality score					
<8	7	0.18 (0.09-0.31)	26.1	<0.01	0.49
8 or greater	3	0.11 (0.07-0.15)			0.13

IB_{EUS}: Incremental benefit of EUS, CT: Computed tomography, MRI: Magnetic resonance imaging

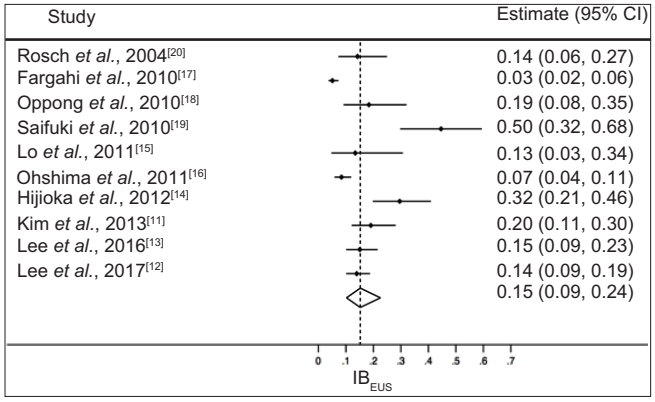

Figure 2. Forest plot of pooled estimate of effect for the incremental benefit of EUS in identifying malignancy after nondiagnostic ERCP. CI: Confidence interval; IB_{EUS}: Incremental benefit of EUS

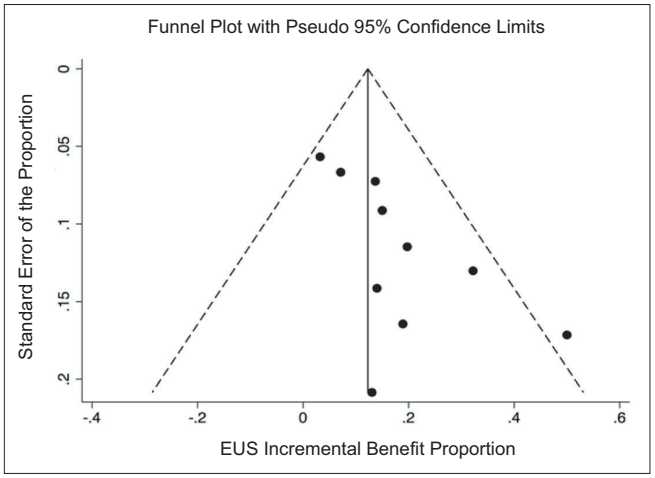

Figure 3. Funnel plot for studies considering the incremental benefit of EUS in identifying malignancy after nondiagnostic ERCP

Individual study analysis

By examining individual reports, two studies yielded noteworthy results. Lee *et al.* described their prospective recruitment and categorization of biliary strictures according to its location – proximal (suprapancreatic) *versus* distal (intrapancreatic) common bile duct.[13] For proximal strictures, if a diagnosis of malignancy was not made on initial ERCP, ERCP with brushings was repeated. For distal strictures, EUS with fine-needle aspiration was performed. In total, 78 proximal-type strictures were identified, of which initial ERCP

was diagnostic in 54 (69%).[13] Twenty-three patients underwent a second ERCP and malignancy was diagnosed in 22 (96%).[13] Of the 42 distal-type strictures identified, initial ERCP diagnosed malignancy in 23 (55%).[13] Nineteen patients underwent subsequent EUS with fine-needle aspiration and malignancy was diagnosed in 18 (94%) patients.[13] Overall, the diagnostic accuracy for the combination of ERCP with the second ERCP for proximal-type strictures and ERCP followed by EUS with fine-needle aspiration for distal-type strictures was 99% and 98%, respectively.[13]

In a later study by Lee *et al.*, consecutive patients were categorized according to the nature of lesion causing the biliary stricture, intrinsic (within bile duct) *versus* extrinsic (outside bile duct).[12] For individuals with intrinsic strictures and nondiagnostic initial ERCP, a second ERCP was performed. For individuals with extrinsic-type strictures and nondiagnostic ERCP, an EUS with fine-needle aspiration was performed. In total, 88 intrinsic biliary strictures were detected, of which initial ERCP detected malignancy in 69 patients (79%).[12] Nineteen patients underwent a second ERCP and 13 (69%) were found to be positive for malignancy.[12] Of the 90 extrinsic biliary strictures, 57 (63%) strictures were diagnosed to be malignant after initial ERCP.[12] Thirty-three patients underwent EUS with fine-needle aspiration after nondiagnostic ERCP, and of these, 26 (79%) were found to be positive for malignancy.[12] The overall sensitivity of this approach for identifying malignancy for intrinsic- and extrinsic-type strictures was 97% and 97%, respectively.[12]

DISCUSSION

In this systematic review and meta-analysis, our results demonstrate that EUS increases the detection of malignancy among patients investigated for extrahepatic biliary strictures and an initial nonmalignant diagnosis on ERCP. The adjusted IB_{EUS} was 14%. This means that a malignant diagnosis will be realized in one of every seven patients who undergo EUS following a nondiagnostic ERCP for an extrahepatic biliary stricture.

Our review supports the contention that a multimodal approach for investigating extrahepatic biliary strictures that includes ERCP and EUS in selected cases increases the opportunity for detecting the underlying malignancy. With a sensitivity of 45% for ERCP brushings alone, other diagnostic modalities are necessary to increase the detection of cancers early in the investigative process.[21] When paired with ERCP, our results show that EUS facilitates the identification and cytopathological confirmation of malignancy to enable timely therapy. It is interesting to note that ERCP and EUS procedures done in tandem yield a higher pooled estimate of effect than when the procedures are done separately.

There is evidence suggesting that EUS may be particularly useful for distal strictures as well as strictures caused by extrinsic mass compressions. A recent meta-analysis demonstrated that the pooled sensitivity and specificity of EUS for the diagnosis of malignant biliary strictures were 80% and 97%, respectively, with higher diagnostic sensitivity in distal strictures.[3] In single study analysis within our systematic review, Lee *et al.* demonstrated that EUS with fine-needle aspiration identified malignancy in 18 out of 19 distal biliary strictures, which were not diagnosed by initial ERCP with brushing cytology.[13] This increased the diagnostic accuracy of ERCP followed by EUS to 98% compared to 60% when ERCP was used alone.[13] In 2017, the same authors demonstrated that a combination approach using ERCP and EUS with fine-needle aspiration increased diagnostic sensitivity for biliary strictures related to extrinsic compression from 68% to 97%.[12] EUS identified malignancy in 26 out of 33 strictures that were not previously diagnosed after an initial ERCP with brushings cytology.[12]

An important consideration is the risk of needle tract seeding leading to metastases. Heimbach *et al.*[22] have demonstrated peritoneal metastases in 83% (5/6) of patients who underwent fine-needle aspiration of unresectable hilar cholangiocarcinoma. Unfortunately, they did not distinguish between percutaneous and EUS approaches. Few studies have examined the risk of seeding among distal common bile duct malignant strictures. Fifteen case reports since 2003 have described needle tract seeding following EUS with fine-needle aspiration of pancreatic neoplasms.[23] Levy *et al.*[24] have also identified malignant cells within the gastrointestinal luminal fluid of 11.5% (3/26) of patients who underwent EUS with fine-needle aspiration of their pancreatic cancer. On the other hand, several retrospective studies have shown contrary evidence, where it does not significantly increase the risk of needle tract seeding.[25-29] The use of EUS with fine-needle aspiration has also not shown to impact overall survival or disease recurrence.[27,30] Overall, based on the evidence to date, EUS with fine-needle

aspiration is not recommended for proximal biliary strictures, whereas the risk associated with distal biliary strictures remains unclear.

Integrating the results of our meta-analysis and concerns for needle tract seeding, we propose a diagnostic approach for patients with suspected malignant biliary strictures, illustrated in Figure 4. Patients' extrahepatic biliary strictures are initially evaluated by cross-sectional imaging such as CT scan or MRI. The stricture is characterized in terms of its location and whether there is a tumor causing the stricture either by intrinsic or extrinsic compression. For proximal strictures not related to extrinsic compression, ERCP with brush cytology is the initial diagnostic modality of choice. If this is not diagnostic for malignancy, ERCP with brushings can be reattempted. Cholangioscopy may also be considered in centers with access to this technology. For distal bile duct strictures or those related to extrinsic compression, EUS may be the initial diagnostic modality of choice and can be performed in tandem with ERCP if necessary for diagnostic and therapeutic purposes. Surgical resection and imaging surveillance can be considered as appropriate for biliary strictures where malignancy has not been identified after multimodality evaluation. The

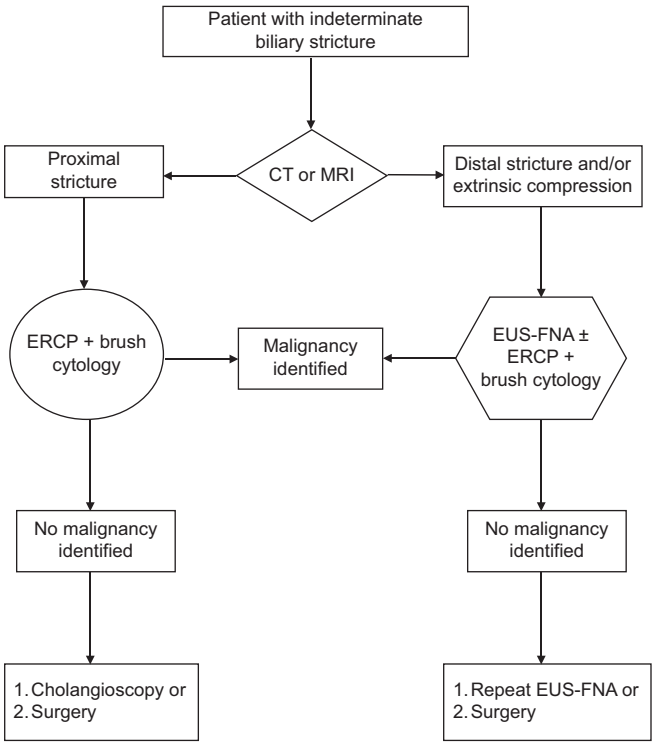

Figure 4. Proposed diagnostic algorithm for the assessment of indeterminate biliary strictures. CT: Computed tomography; MRI: Magnetic resonance imaging

complementary role of EUS to aid in the diagnostic workup for distal biliary strictures has recently been suggested in a review by Bowlus *et al*.[31] Prospective studies are needed to validate this algorithm.

There are some limitations of this study. First, the quality of the studies was variable. Almost half of the included studies were abstracts and half of the studies examined were retrospective and therefore prone to bias. Second, small-study effects were noted. This was addressed by correcting the IB_{EUS} estimate for small-study effects using the trim-and-fill method and performing stratified analyses based on the study size, which yielded more conservative estimates. Third, there was heterogeneity among the studies, which could reflect design diversity, especially with varying procedures to identify stricture location and the role of EUS in the included studies. To address this, a random effects model was utilized for pooled estimate of effect. In addition, stratified analyses were performed to identify sources of heterogeneity and how these characteristics affected the pooled estimate of effect. Finally, some factors that have been shown to influence the diagnostic yield (such as the use of fluorescence *in situ* hybridization) were not measured in the included studies, and this could influence the impact of EUS. Future research in this area will be needed, including large prospective trials that include the impact of procedural and pathology specimen evaluation protocols.

CONCLUSION

This systematic review demonstrates that EUS is an invaluable diagnostic tool following ERCP to help identify malignancy in patients with extrahepatic biliary strictures. EUS can help establish a diagnosis in one of every seven cases of indeterminate biliary strictures. This impact is likely even greater for patients with distal strictures or those related to masses causing extrinsic compression. ERCP and EUS performed in tandem may be ideal for patient and resource management if biliary stenting is required. Large prospective studies are needed to establish the efficacy of multimodal approaches in the evaluation of extrahepatic biliary strictures to maximize the diagnostic yield in a timely fashion.

Supplementary materials

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Brandi G, Venturi M, Pantaleo MA, *et al.* Cholangiocarcinoma: Current opinion on clinical practice diagnostic and therapeutic algorithms: A review of the literature and a long-standing experience of a referral center. *Dig Liver Dis* 2016;48:231-41.
2. Navaneethan U, Njei B, Lourdusamy V, *et al.* Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: A systematic review and meta-analysis. *Gastrointest Endosc* 2015;81:168-76.
3. Sadeghi A, Mohamadnejad M, Islami F, *et al.* Diagnostic yield of EUS-guided FNA for malignant biliary stricture: A systematic review and meta-analysis. *Gastrointest Endosc* 2016;83:290-80.
4. Eloubeidi MA, Chen VK, Jhala NC, *et al.* Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2004;2:209-13.
5. Fritscher-Ravens A, Broering DC, Knoefel WT, *et al.* EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. *Am J Gastroenterol* 2004;99:45-51.
6. Prospero, International Prospective Register of Systematic Reviews. Available from: https://www.crd.york.ac.uk/prospero/. [Last accessed on 2018 Apr 22].
7. Shamseer L, Moher D, Clarke M, *et al.* Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* 2015;350:g7647.
8. James PD, Meng ZW, Zhang M, *et al.* The incremental benefit of EUS for identifying unresectable disease among adults with pancreatic adenocarcinoma: A meta-analysis. *PLoS One* 2017;12:e0173687.
9. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Otawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses; 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Last accessed on 2018 Jul 18].
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
11. Kim DC, Moon JH, Choi HJ, *et al.* The role of EUS-FNA after negative endoscopic transpapillary forceps biopsy in patients with malignant biliary strictures. *Gastrointest Endosc* 2013;77:AB422.
12. Lee YN, Moon JH, Choi HJ, *et al.* Diagnostic approach using ERCP-guided transpapillary forceps biopsy or EUS-guided fine-needle aspiration biopsy according to the nature of stricture segment for patients with suspected malignant biliary stricture. *Cancer Med* 2017;6:582-90.
13. Lee YN, Moon JH, Choi HJ, *et al.* Diagnostic approach using peroral cholangioscopy-guided forceps biopsy or EUS-guided fine-needle aspiration biopsy according to the location of stricture for patients with suspected malignant biliary stricture: A prospective comparative study. *Gastrointest Endosc* 2016;83:AB125-6.
14. Hijioka S, Hara K, Mizuno N, *et al.* Diagnostic yield of endoscopic retrograde cholangiography and of EUS-guided fine needle aspiration sampling in gallbladder carcinomas. *J Hepatobiliary Pancreat Sci* 2012;19:650-5.
15. Lo DY, Howell DA, Wright E, *et al.* Su1429 frozen section of ERCP Forceps biopsy specimens permits efficient intraprocedural diagnosis. *Gastrointest Endosc* 2011;73:AB263.
16. Ohshima Y, Yasuda I, Kawakami H, *et al.* EUS-FNA for suspected malignant biliary strictures after negative endoscopic transpapillary brush cytology and forceps biopsy. *J Gastroenterol* 2011;46:921-8.
17. Fargahi S, Lee J, Lin F, *et al.* Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in the cytologic diagnosis of cholangiocarcinoma – A comparative and morphologic study. *Cancer Cytopathol* 2010;118:323.
18. Oppong K, Raine D, Nayar M, *et al.* EUS-FNA versus biliary brushings and assessment of simultaneous performance in jaundiced patients with suspected malignant obstruction. *JOP* 2010;11:560-7.
19. Saifuku Y, Yamagata M, Koike T, *et al.* Endoscopic ultrasonography can diagnose distal biliary strictures without a mass on computed tomography. *World J Gastroenterol* 2010;16:237-44.
20. Rösch T, Hofrichter K, Frimberger E, *et al.* ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. *Gastrointest Endosc* 2004;60:390-6.
21. Paranandi B, Oppong KW. Biliary strictures: Endoscopic assessment and management. *Frontline Gastroenterol* 2017;8:133-7.
22. Heimbach JK, Sanchez W, Rosen CB, *et al.* Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *HPB* (Oxford) 2011;13:356-60.
23. Minaga K, Takenaka M, Katanuma A, *et al.* Needle tract seeding: An overlooked rare complication of endoscopic ultrasound-guided fine-needle aspiration. *Oncology* 2017;93 Suppl 1:107-12.
24. Levy MJ, Gleeson FC, Campion MB, *et al.* Prospective cytological assessment of gastrointestinal luminal fluid acquired during EUS: A potential source of false-positive FNA and needle tract seeding. *Am J Gastroenterol* 2010;105:1311-8.
25. Ngamruengphong S, Xu C, Woodward TA, *et al.* Risk of gastric or peritoneal recurrence, and long-term outcomes, following pancreatic cancer resection with preoperative endosonographically guided fine needle aspiration. *Endoscopy* 2013;45:619-26.
26. Ikezawa K, Uehara H, Sakai A, *et al.* Risk of peritoneal carcinomatosis by endoscopic ultrasound-guided fine needle aspiration for pancreatic cancer. *J Gastroenterol* 2013;48:966-72.
27. El Chafic AH, Dewitt J, Leblanc JK, *et al.* Impact of preoperative endoscopic ultrasound-guided fine needle aspiration on postoperative recurrence and survival in cholangiocarcinoma patients. *Endoscopy* 2013;45:883-9.
28. Yoon WJ, Daglilar ES, Fernández-del Castillo C, *et al.* Peritoneal seeding in intraductal papillary mucinous neoplasm of the pancreas patients who underwent endoscopic ultrasound-guided fine-needle aspiration: The PIPE study. *Endoscopy* 2014;46:382-7.
29. Tsutsumi H, Hara K, Mizuno N, *et al.* Clinical impact of preoperative endoscopic ultrasound-guided fine-needle aspiration for pancreatic ductal adenocarcinoma. *Endosc Ultrasound* 2016;5:94-100.
30. Ngamruengphong S, Swanson KM, Shah ND, *et al.* Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer. *Gut* 2015;64:1105-10.
31. Bowlus CL, Olson KA, Gershwin ME. Evaluation of indeterminate biliary strictures. *Nat Rev Gastroenterol Hepatol* 2016;13:28-37.

Supplementary Table 1. Search strategy

Search Strategy - Medline

Term No.	MeSH Term	No. Hits
1	exp bile duct diseases/or biliary tract neoplasms/	174047
2	(bile adj3 (cancer or neoplasm* or malignan* or carcinoma)).tw.	7433
3	exp Bile Ducts, Extrahepatic/	27564
4	((bile or biliary) adj3 stricture*).tw.	9336
5	Cholangiocarcinoma/	16364
6	(Cholangiocellular carcinoma or Cholangiocarcinoma).tw.	22435
7	Cholestasis.tw.	30385
8	(biliary adj (Atresia or obstruction)).tw.	19242
9	or/1-8	210704
10	Endosonography/	30779
11	endosonography.tw.	3822
12	(endoscop* adj2 (ultrasound or ultrason* or sonogra*)).tw.	24967
13	ultrasonography, interventional/	38750
14	biopsy/or endoscopic ultrasound-guided fine needle aspiration/	329328
15	(eus or biops*).tw.	860953
16	or/10-15	1015618
17	9 and 16	19959
18	Cholangiopancreatography, Endoscopic Retrograde/	45680
19	ercp.tw.	23460
20	endoscop* cholangiopancreatograph*.tw.	250
21	endoscop* retrograde cholangiopancreatograph*.tw.	15853
22	or/18-21	52584
23	17 and 22	4896
24	23 use ppez	1517

Search Strategy - Embase

Term No.	MeSH Term	No. Hits
25	exp *bile duct disease/	108399
26	exp *biliary tract tumor/	23766
27	hepatic duct/	7323
28	((bile or biliary) adj3 stricture*).tw.	9336
29	(Cholangiocellular carcinoma or Cholangiocarcinoma).tw.	22435
30	Cholestasis.tw.	30385
31	*cholestasis/	23043
32	(biliary adj (Atresia or obstruction)).tw.	19242
33	(bile adj3 (cancer or neoplasm* or malignan* or carcinoma)).tw.	7433
34	or/25-33	158618
35	endoscopic echography/	22890
36	endosonography.tw.	3822
37	(endoscop* adj2 (ultrasound or ultrason* or sonogra*)).tw.	24967
38	biopsy/	327441
39	endoscopic ultrasound guided fine needle biopsy/	2139
40	(eus or biops*).tw.	860953
41	or/35-40	997604
42	34 and 41	15310
43	endoscopic retrograde cholangiopancreatography/	45680
44	ercp.tw.	23460
45	endoscop* cholangiopancreatograph*.tw.	250
46	endoscop* retrograde cholangiopancreatograph*.tw.	15853
47	or/43-46	52584
48	42 and 47	3730
49	48 use emczd	2482

Search Strategy - Cochrane

Term No.	Term	No. Hits
50	exp bile duct diseases/or biliary tract neoplasms/	174047
51	(bile adj3 (cancer or neoplasm* or malignan* or carcinoma)).tw, kw.	8140
52	exp Bile Ducts, Extrahepatic/	27564
53	((bile or biliary) adj3 stricture*).tw, kw.	9509
54	Cholangiocarcinoma/	16364
55	(Cholangiocellular carcinoma or Cholangiocarcinoma).tw, kw.	23082
56	Cholestasis.tw.	30385
57	(biliary adj (Atresia or obstruction)).tw, kw.	19445
58	or/50-57	211205
59	Endosonography/	30779
60	endosonography.tw, kw.	4496
61	(endoscop* adj2 (ultrasound or ultrason* or sonogra*)).tw, kw.	25527
62	ultrasonography, interventional/	38750
63	biopsy/or endoscopic ultrasound-guided fine needle aspiration/	329328
64	(eus or biops*).tw, kw.	868421
65	or/59-64	1021019
66	58 and 65	20096
67	Cholangiopancreatography, Endoscopic Retrograde/	45680
68	ercp.tw, kw.	24031
69	endoscop* cholangiopancreatograph*.tw, kw.	690
70	endoscop* retrograde cholangiopancreatograph*.tw, kw.	16673
71	or/67-70	52977
72	66 and 71	4985
73	72 use cctr	46

Search strategy combined

Term No.	Term	No. Hits
74	24 or 49 or 73	4045
75	remove duplicates from 74	3131
76	75 use ppez (1484) Medline	
77	75 use emczd (1644) Embase	
78	75 use cctr (3) Cochrane	

*: A truncation symbol to search on the root of that term and all of its endings

Contd...