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 (IBEUS) 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 IBEUS estimate with the adjustment for publication bias was 14% (95% confidence interval, 7%-20%). Individual studies demonstrate that the IBEUS 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...
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\textsubscript{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.[8] 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\textsubscript{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\textsubscript{EUS} which was expressed as IB\textsubscript{EUS} = (N\textsubscript{EUS}/T\textsubscript{ERCP}), where T\textsubscript{ERCP} is the total number of patients who underwent ERCP with brushings for suspected malignant biliary strictures and N\textsubscript{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. 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. IB\textsubscript{EUS} and its variance were represented using the logit of proportion (IP). For sample size proportional weighting, the standard error of each study was calculated. The IP was summarized across studies using a random effects model and the methods proposed by DerSimonian and Laird. The IP was then converted to the IB\textsubscript{EUS} and the corresponding 95% confidence interval (CI). Small-study effects and publication bias were evaluated through the visual inspection of funnel plots and Begg’s asymmetry test.

Heterogeneity of IB\textsubscript{EUS} across studies was assessed via the inspection of asymmetry among forest plots and calculation of the \( I^2 \) inconsistency statistic.

Meta-analyses and meta-regression of the study characteristics were performed to evaluate its effects on pooled estimates of effects. \textit{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. 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.

**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.
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%).

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**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 [14] | Unknown      | South Korea   | Prospective  | 76                       | Unknown             | 76                                 | 17                            | 15                                           |
| Hijioka et al., 2012 [15] | 2001-2010    | Japan          | Retrospective | 83                       | 64.8                | 59                                 | 19                            | 19                                           |
| Lo et al., 2011 [16] | Unknown      | USA            | Prospective  | 23                       | 66                  | 23                                 | 8                             | 3                                            |
| Ohshima et al., 2011 [17] | 2007-2009    | Japan          | Retrospective | 225                      | 71.5                | 225                                | 22                            | 16                                           |
| Fargahi et al., 2010 [18] | 1998-2009    | USA            | Retrospective | 311                      | Unknown             | 311                                | 75                            | 10                                           |
| Oppong et al., 2010 [19] | 2004-2007    | United Kingdom | Prospective  | 38                       | 62.4                | 37                                 | 37                            | 7                                            |
| Saifuku et al., 2010 [20] | 2005-2008    | Japan          | Retrospective | 34                       | 71                  | 34                                 | 34                            | 17                                           |
| Rösch et al., 2004 [21] | 1998-2000    | Germany        | Prospective  | 50                       | 62.1                | 50                                 | 50                            | 7                                            |

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

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**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 [14] | Yes              | No                 | Yes                  | Yes                   | Yes                     | No                            | Yes                      | Yes                 | Yes               | 7             |
| Hijioka et al., 2012 [15] | Yes              | No                 | Yes                  | Yes                   | No                      | No                            | Yes                      | Yes                 | Yes               | 6             |
| Lo et al., 2011 [16] | Yes              | No                 | Yes                  | Yes                   | No                      | No                            | Yes                      | Yes                 | Yes               | 6             |
| Ohshima et al., 2011 [17] | Yes              | No                 | Yes                  | Yes                   | Yes                     | Yes                           | Yes                      | Yes                 | Yes               | 8             |
| Fargahi et al., 2010 [18] | Yes              | No                 | Yes                  | Yes                   | No                      | No                            | Yes                      | Yes                 | Yes               | 6             |
| Oppong et al., 2010 [19] | Yes              | No                 | Yes                  | Yes                   | No                      | No                            | Yes                      | Yes                 | Yes               | 6             |
| Saifuku et al., 2010 [20] | Yes              | No                 | Yes                  | Yes                   | Yes                     | Yes                           | Yes                      | Yes                 | Yes               | 7             |
| Rösch et al., 2004 [21] | Yes              | No                 | Yes                  | Yes                   | Yes                     | Yes                           | Yes                      | Yes                 | Yes               | 8             |
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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 I² statistics (%) | t² 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|

IBEUS: 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; IBEUS: Incremental benefit of EUS

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%).[13] 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.[13] 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 nondiagnostic 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 cytological 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.[23-29] 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
Integration 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.

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.

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### 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/ ((bile or biliary) adj3 stricture*).tw. | 27564    |
| 4        | Cholangiocarcinoma/ (Cholangiocellular carcinoma or Cholangiocarcinoma).tw. | 16364    |
| 5        | Cholestasis.tw. | 30385    |
| 6        | (biliary adj (Atresia or obstruction)).tw. | 9336     |
| 7        | Endosonography/ | 210704   |
| 8        | (endoscop* adj2 (ultrasound or ultrason* or sonogra*)).tw. | 24967    |
| 9        | ultrasonography, interventional/ | 38750    |
| 10       | biopsy/or endoscopic ultrasound-guided fine needle aspiration/ (eus or biops*).tw. | 329328   |
| 11       | or/10-15  | 1015618  |
| 12       | 9 and 16  | 19959    |
| 13       | Cholangiopancreatography, Endoscopic Retrograde/ | 45680    |
| 14       | ercp.tw.  | 23460    |
| 15       | endoscop* cholangiopancreatograph*.tw. | 250      |
| 16       | endoscop* retrograde cholangiopancreatograph*.tw. | 15853    |
| 17       | or/18-21  | 52584    |
| 18       | 17 and 22 | 4896     |
| 19       | 23 use ppez | 1517     |
| 20       | Cholangiopancreatography, Endoscopic Retrograde/ | 45680    |
| 21       | ercp.tw.  | 23460    |
| 22       | endoscop* cholangiopancreatograph*.tw. | 250      |
| 23       | endoscop* retrograde cholangiopancreatograph*.tw. | 15853    |
| 24       | or/18-21  | 52584    |
| 25       | 17 and 22 | 4896     |
| 26       | 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/ (eus or biops*).tw. | 860953   |
| 40       | or/35-40  | 997604   |
| 41       | 34 and 41 | 15310    |

#### Search Strategy - Cochrane

| Term No. | MeSH 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/ ((bile or biliary) adj3 stricture*).tw, kw. | 27564    |
| 53       | Cholangiocarcinoma/ | 16364    |
| 54       | (Cholangiocellular carcinoma or Cholangiocarcinoma).tw, kw. | 23082    |
| 55       | Cholestasis.tw. | 30385    |
| 56       | (biliary adj (Atresia or obstruction)).tw, kw. | 19445    |
| 57       | or/50-57  | 211205   |
| 58       | Endosonography/ | 30779    |
| 59       | endosonography,tw, kw. | 4496     |
| 60       | (endoscop* adj2 (ultrasound or ultrason* or sonogra*)).tw, kw. | 25527    |
| 61       | ultrasonography, interventional/ | 38750    |
| 62       | biopsy/or endoscopic ultrasound-guided fine needle aspiration/ (eus or biops*).tw, kw. | 329328   |
| 63       | or/59-64  | 1021019  |
| 64       | 58 and 65 | 20096    |
| 65       | Cholangiopancreatography, Endoscopic Retrograde/ | 45680    |
| 66       | ercp.tw.  | 23460    |
| 67       | endoscop* cholangiopancreatograph*.tw. | 250      |
| 68       | endoscop* retrograde cholangiopancreatograph*.tw. | 15853    |
| 69       | or/67-70  | 52977    |
| 70       | 66 and 71 | 4985     |
| 71       | 72 use cctr | 46       |

#### Search strategy combined

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

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

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