Diagnostic yield of EUS-guided FNA for malignant biliary stricture: a systematic review and meta-analysis CME

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Background and Aims: EUS-guided FNA (EUS-FNA) is increasingly being used for tissue diagnosis of extrahepatic biliary strictures. The aim of this study was to determine the diagnostic yield of EUS-FNA in malignant biliary strictures.

Methods: A comprehensive literature review was carried out by 2 reviewers for studies evaluating the accuracy of EUS-FNA in biliary stricture. A meta-analysis was performed to determine the pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio for EUS-FNA of extrahepatic biliary stricture. A Quality Assessment of Diagnostic Accuracy Studies questionnaire was used to assess the quality of the selected studies. Several sensitivity analyses were performed to assess the effect of the quality of the studies on the accuracy of the final results of the meta-analysis.

Results: Twenty studies involving 957 patients met inclusion criteria and were included in the meta-analysis. The pooled sensitivity and specificity of EUS-FNA for diagnosis of malignant biliary stricture were 80% (95% confidence interval [CI], 74%-86%), and 97% (95% CI, 94%-99%), respectively. The pooled positive likelihood ratio was 12.35 (95% CI, 7.37-20.72), and the negative likelihood ratio was 0.26 (95% CI, 0.18-0.38). The pooled diagnostic odds ratio for diagnosing a malignant biliary stricture was 70.53 (95% CI, 38.62-128.82). The area under the receiver-operating characteristic curve was 0.97. Sensitivity analyses showed that the quality of the included studies did not affect the accuracy of the final results of the meta-analysis.

Conclusion: This meta-analysis demonstrates that EUS-FNA is sensitive and highly specific for diagnosing malignancy in biliary strictures. Further studies are needed to compare EUS–FNA with emerging methods including cholangioscopy-guided biopsy and laser endomicroscopy. (Gastrointest Endosc 2016;83:290-8.)

Extrahepatic biliary strictures pose a major challenge for gastroenterologists and pancreaticobiliary surgeons alike. There is a broad differential diagnosis for biliary stricture including benign or malignant intrinsic lesions and extrinsic compression from benign or malignant conditions.[1]

Transabdominal US and CT can reveal dilation of the upstream bile ducts in biliary strictures. However, they cannot provide definitive diagnosis in most patients with biliary strictures. Tumor markers including carbohydrate antigen 19-9 have only modest sensitivity and specificity for diagnosing malignancy in biliary strictures.[2] Furthermore, brushing the stricture during ERCP has poor sensitivity and low negative predictive value for diagnosing malignancy.[3,4]

The common bile duct is closely apposed to the first and second portions of duodenum and is readily accessible on EUS examination. EUS-guided FNA (EUS-FNA) is increasingly being used for tissue diagnosis of extrahepatic biliary strictures. There is a significant variability in the reported sensitivity and predictive values of EUS-guided FNA in biliary strictures across different studies. To our knowledge, there has not been any formal quantitative and comprehensive literature review to determine sensitivity, specificity, and predictive values of EUS-guided FNA in diagnosing malignancy in biliary strictures. The aim of this study was to perform a structured systematic review and meta-analysis of all relevant studies to determine the diagnostic utility of EUS-guided FNA in malignant biliary strictures.

Abbreviations: CI, confidence interval; EUS-FNA, EUS-guided FNA.

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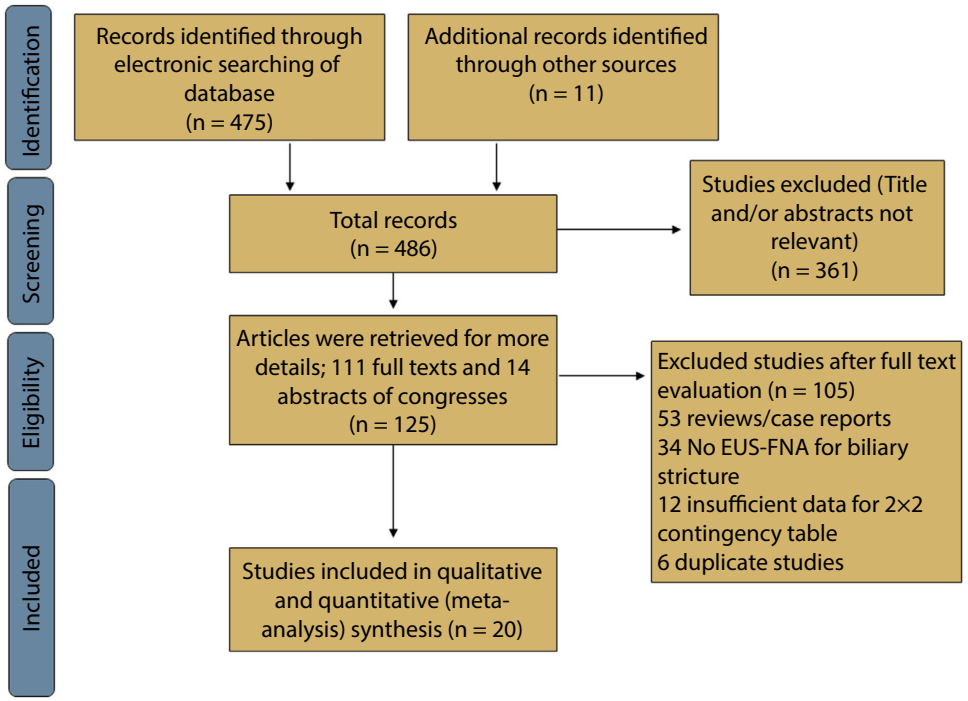

Figure 1. Flow diagram of the study.

METHODS

Protocol and registration

This was a systematic literature review and meta-analysis of studies reporting diagnostic yield of EUS-guided FNA for malignant biliary stricture. The study protocol was prospectively registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42014013907).

Study selection criteria

Studies investigating the utility of EUS-FNA for detection of malignancy in biliary strictures were included. Only studies with data available for the construction of a 2 x 2 contingency table were included. The criterion standards for the diagnosis of cancer in all of the studies were based on tissue diagnosis or long-term follow-up. No study was excluded based on the language of publication, quality of study, or country of origin. The exclusion criteria were review articles, editorials, letter to editors, case reports and case series with fewer than 10 patients, and studies containing insufficient data to construct 2 x 2 contingency table. Authors of the articles with inadequate data were contacted through email to request unavailable data.

Information sources. A comprehensive search of the literature was performed to identify articles that examined the diagnostic accuracy of EUS-FNA for malignant biliary strictures. We systematically searched PubMed, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials and Database of Systematic Reviews up to June 2014. Additionally, abstracts from major gastroenterology conferences in the past 7 years (including Digestive Disease Week, the annual meeting of American College of Gastroenterology, and United European Gastroenterology Week) were searched. Also, reference lists of retrieved articles, reviews, and meta-analyses for additional articles were hand-searched to find additional eligible studies. The search terms used were Cholangiocarcinoma(s) OR Cholangiocellular carcinoma(s) OR Biliary Stricture(s) OR Biliary Obstruction(s) OR Extrahepatic Cholestasis AND Endoscopic ultrasonography OR EUS-FNA OR EUS-guided-FNA OR EUS-guided fine needle aspiration OR FNA biopsy OR Interventional endoscopic ultrasonography OR Endosonography.

The titles and abstracts of all search results were reviewed independently by 2 of the authors (M.M., S.A.) to determine whether the literature was relevant according to the inclusion criteria. Full-text articles that did not fulfill the predefined criteria were excluded. The differences were resolved by mutual agreement or consultation with the third reviewer (M.A.E.). A flow diagram of the study is presented in Figure 1.

Quality of studies

The Quality Assessment of Diagnostic Accuracy Studies questionnaire was used to assess the quality of the selected studies.[5] Based on this questionnaire, 14 items were assessed for each article, and the items were rated as yes, no, or unclear.

Sensitivity analysis

A sensitivity analysis was performed to test whether a single study had undue influence on the study results. We used the jackknife method for sensitivity analysis.[6] In this method, we successively removed 1 study at a time and recalculated the pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio for the remaining studies to see whether there was a significant change in test performance. A meta-regression analysis was conducted to determine whether quality scores of the studies affected the diagnostic accuracy of EUS-FNA in biliary strictures.

Statistical analysis

For each study, a 2 × 2 contingency table consisting of true-positive, false-positive, true-negative, and false-negative results was constructed. A meta-analysis of the diagnostic accuracy of EUS-FNA in malignant biliary strictures was performed by calculating pooled estimates of sensitivity, specificity, diagnostic odds ratio, and negative and positive likelihood ratios.

We constructed receiver-operating characteristic curves to summarize the study results by the Moses-Shapiro-Littenberg method.[7] We also assessed the diagnostic yields of EUS-FNA in bile duct malignancies excluding extrinsic compression on bile ducts by pancreatic masses. In the next step, we examined the diagnostic accuracy of EUS-FNA in proximal and distal biliary strictures separately. Deeks' funnel plot was conducted to detect publication bias.[8]

Heterogeneity was assessed by using χ^2 statistics and the I^2 measure of inconsistency. Analyses were performed with Meta-DiSc Version 1.4 (Clinical Biostatistics Unit, Ramón y Cajal Hospital, Madrid, Spain) and Stata Release 13 (StataCorp, College Station, Tex).

RESULTS

Eligible studies and quality assessment

The original search generated 475 studies. An additional 11 studies were identified through a manual search of other sources. The titles and abstracts of these studies were reviewed. According to predefined exclusion criteria, 361 studies were excluded and 125 articles were reviewed in depth. Of these, 20 studies (957 patients) were included in the final analysis.[9-28] One non-English study[18] was translated from Portuguese by Google Translate. Figure 1 demonstrates the flow diagram of the search results. Table 1 lists the studies included in the meta-analysis.

Sixteen studies[9-14,16,18-23,26-28] were published as full text in peer-reviewed journals, and 4 studies[15,17,24,25] were published as abstracts in major conferences. The qualities of the relevant studies as assessed by Quality Assessment of Diagnostic Accuracy Studies criteria are shown in Figure 2.

Synthesis of results

Malignant biliary stricture. The pooled sensitivity and specificity of EUS-FNA for the diagnosis of malignant biliary strictures were 80% (95% confidence interval [CI], 74%-86%), and 97% (95% CI, 94%-99%) respectively (Figs. 3 and 4).

The pooled positive likelihood ratio was 12.35 (95% CI, 7.37-20.72), and the pooled negative likelihood ratio was 0.26 (95% CI, 0.18-0.38).

The pooled diagnostic odds ratio for diagnosing malignant biliary strictures was 70.53 (95% CI, 38.62-128.82). The area under the receiver-operating characteristic curve was 0.97, and the Q* index was 0.92 (Fig. 5).

The overall heterogeneity indices of I^2 measure of inconsistency were 78%.

In the next step, we assessed the utility of EUS-FNA in diagnosing biliary malignancies after excluding biliary strictures in the setting of extrinsic compression of pancreatic head cancer. Fifteen studies (including 502 patients) reported the diagnostic yield of EUS-FNA in bile duct malignancies excluding extrinsic compression on bile ducts by pancreatic masses.

The pooled sensitivity and specificity were 79% (95% CI, 72%-86%) and 99% (95% CI, 95%-100%), respectively. The diagnostic odds ratio was 47.34 (95% CI, 20.65-108.53).

Distal versus proximal biliary strictures. In this analysis, we calculated the diagnostic accuracy of EUS-FNA for distal and proximal biliary strictures separately. Some of the studies reported the diagnostic accuracies of EUS-FNA in biliary strictures in general and did not report the respective values for distal and proximal strictures separately.

Nine studies (including 294 patients) reported sensitivity of EUS-FNA in proximal biliary strictures, whereas 4 studies (including 158 patients) reported the diagnostic value of EUS-FNA exclusively in distal biliary strictures.

The pooled sensitivity of EUS-FNA for distal and proximal biliary strictures were 83% (95% CI, 68%-98%) and 76% (95% CI, 66%-85%), respectively. The pooled specificity of EUS-FNA in distal and proximal biliary strictures was 100% (95% CI, 63%-100%) and 100% (95% CI, 95%-100%), respectively. The pooled positive likelihood ratio for distal strictures was 6.93 (95% CI, 1.08-44.54), whereas it was 13.05 (95% CI, 4.34-39.18) for proximal biliary strictures. The pooled negative likelihood ratio for distal strictures was 0.20 (95% CI, 0.02-1.66), whereas it was 0.31 (95% CI, 0.21-0.45) for proximal biliary strictures. The pooled diagnostic odds ratio for distal and proximal biliary strictures was 33.88 (95% CI, 3.59-319.52) and 47.78 (95% CI, 14.02-162.84), respectively.

Adverse events of EUS-FNA. We looked for the adverse event rate of EUS-FNA in the included studies. Nine of the 20 studies did not report the occurrence of adverse events. Eleven studies reported the occurrence of adverse events.[9,10,13,16,18-22,26,28] There were 4 adverse

TABLE 1. Characteristics of the included studies

Authors	Year	Full text versus abstract	Country	Prospective versus retrospective	No. of patients	% Men	Mean age ± SD (range)	On-site cytology	Sensitivity of EUS-FNA, %
Byrne et al[9]	2004	Full text	USA	Retrospective	23	ND*	ND*	Yes	46
Eloubeidi et al[10]	2004	Full text	USA	Prospective	25	72	67 ± 11	Yes	86
Fritscher-Ravens et al[11]	2004	Full text	Germany	Prospective	44	70	59	No	89
Lee et al[12]	2004	Full text	USA	Retrospective	23	ND*	ND*	Yes	47
DeWitt et al[13]	2006	Full text	USA	Retrospective	24	58	68 (37-87)	Yes	77
Meara et al[14]	2006	Full text	USA	Prospective	43	64	66 (37-84)	Yes	87
Agarwal et al[15]	2007	Abstract	USA	Retrospective	21	62	62 ± 16 (23-87)	Yes	62
Ascunce et al[16]	2010	Full text	USA	Retrospective	28	ND*	ND*	Yes	96
Fargahi et al[17]	2010	Abstract	USA	Retrospective	28	ND*	ND*	ND	63
Novis et al[18]	2010	Full text	Brazil	Prospective	41	46	56 (40-87)	No	69
Oppong et al[19]	2010	Full text	UK	Retrospective	39	55	62 (26-87)	No	53
Mohamadnejad et al[20]	2011	Full text	USA	Retrospective	74	56	70 (43-93)	Yes	73
Nayar et al[21]	2011	Full text	UK	Retrospective	31	53	67 (47-87)	No	52
Ohshima et al[22]	2011	Full text	Japan	Retrospective	22	55	72 (53-79)	No	100
Krishna et al[23]	2012	Full text	USA	Retrospective	28	61	62 (23-87)	Yes	67
Putta, et al[24]	2012	Abstract	UK	Retrospective	95	ND*	ND*	ND	78
De la Mora Levy, et al[25]	2013	Abstract	Mexico	Prospective	17	ND*	ND*	ND	94
Nguyen, et al[26]	2013	Full text	Australia	Prospective	25	ND*	ND*	No	91
Tummala, et al[27]	2013	Full text	USA	Retrospective	342	51	68 ± 13	Yes	92
Weilert, et al[28]	2014	Full text	USA	Prospective	51	57	67 (42-88)	Yes	94

ND, Not determined.
*Information was provided for all of the study population; however, it was not specifically given for the subgroup of patients who underwent EUS-guided FNA for biliary stricture.

events reported in the 11 studies involving 383 patients. Three of the adverse events were mild and included self-controlled bleeding (pooled rate of adverse events: 1%; 95% CI, 0.29%-2.65%). There was 1 severe adverse event (biliary peritonitis and procedure-related death)[18] (pooled rate of major adverse events: 0.3%; 95% CI, 0.01%-1.45%).

Sensitivity analysis

A jackknife sensitivity analysis revealed that successive removal of 1 study at a time did not change the diagnostic accuracy of the remaining studies (Supplementary Table 1, available online at www.giejournal.org). This indicates that no single study affected the pooled test performance.

In the next step, we removed the 4 studies published in the abstract form and repeated analyses of the 16 studies with the full text published. The sensitivity of EUS-FNA in the 16 studies published in full text was 80% (95% CI, 73%-87%). This was not different from the calculated sensitivity of 80% observed in all 20 studies together.

We also observed that 10 of 20 studies only considered a definitive positive cytology report as malignancy and regarded highly suspicious cytology as negative for malignancy. We repeated the analysis of these 10 studies. In this subgroup, the sensitivity of EUS-FNA was 82% (95% CI, 78%-86%) for diagnosing malignancy.

To assess the impact of the qualities of the studies on the final results, we performed several sensitivity analyses.

We assessed the diagnostic accuracy of EUS-FNA in studies of higher quality as defined by quality scores of 10 or higher on the Quality Assessment of Diagnostic Accuracy Studies questionnaire. The sensitivity of EUS-FNA was 75% (95% CI, 54%-96%) in the 3 studies[20,21,28] of higher quality.

We also calculated the sensitivity of EUS-FNA in larger studies as defined by sample sizes of more than 25. The sensitivity of EUS-FNA was 79% (95% CI, 70%-87%) in the 12 studies[11,14,16-21,23,24,27,28] with larger sample sizes. This is comparable to the sensitivity of 80% observed in all 20 studies together.

We compared the sensitivity of EUS-FNA in studies from U.S. centers and non-U.S. centers. The sensitivity of EUS-FNA in the studies from the U.S. centers was 79% (95% CI, 72%-87%) and 80% (95% CI, 69%-91%) in the studies from non-U.S. centers.

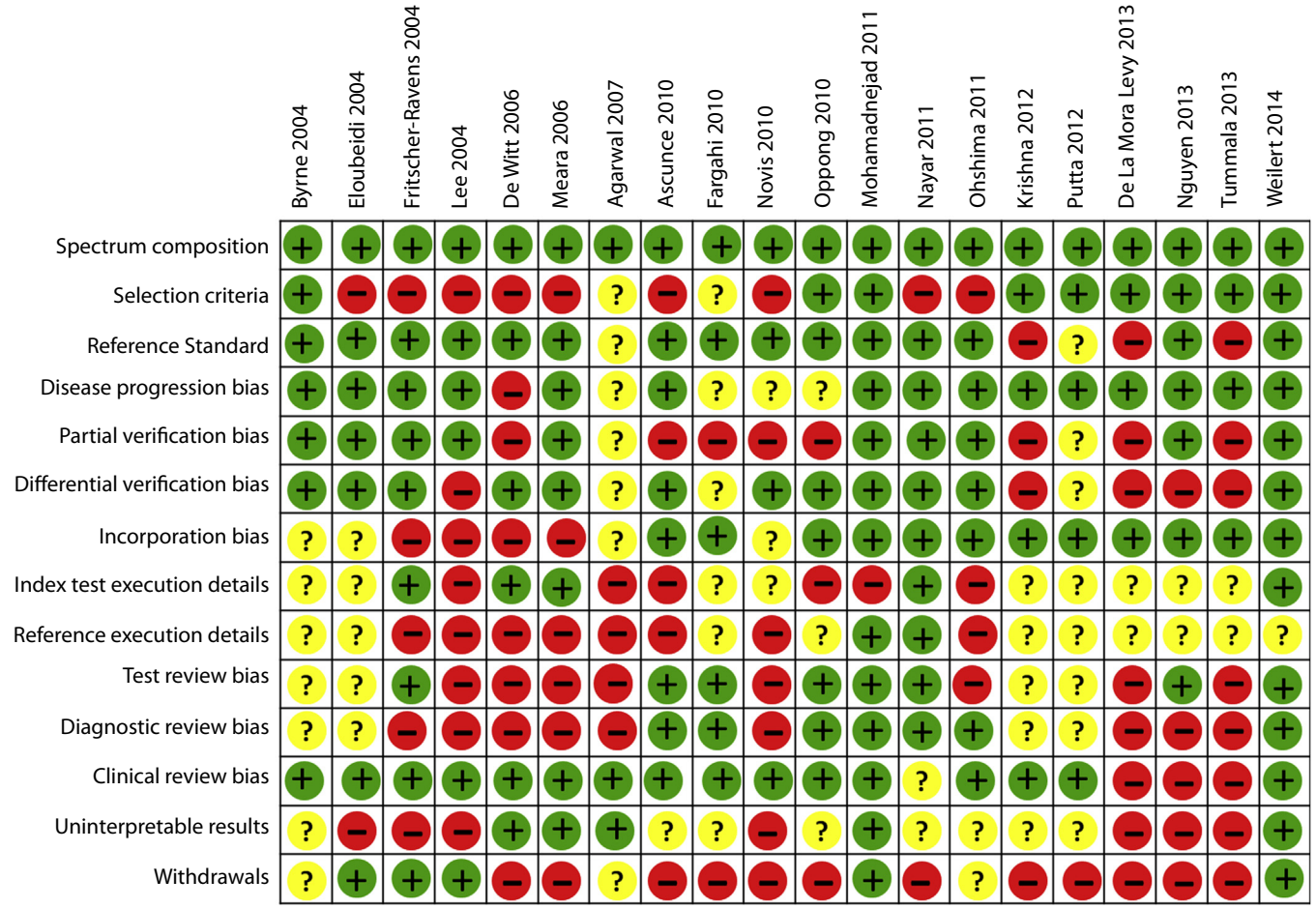

Figure 2. Quality of the studies as assessed by Quality Assessment of Diagnostic Accuracy Studies questionnaire. Green indicates absence of bias, red indicates the presence of bias, and yellow indicates unclear.

We also performed sensitivity analyses of the prospective studies. The sensitivity of EUS-FNA in the prospective studies was 89% (95% CI, 83%-94%). The I^2 was 26.8% in the prospective studies, indicating low heterogeneity in the prospective studies.

Furthermore, a meta-regression analysis demonstrated that the quality scores of the studies did not affect the sensitivity and specificity of EUS-FNA in biliary strictures ($P = .83$ for sensitivity, and $P = .4$ for specificity).

Publication bias

We observed asymmetry in the Deeks' funnel plot (data not shown). This suggests the presence of publication bias.

DISCUSSION

Indeterminate biliary strictures remain a major diagnostic challenge.

Acquisition of a tissue diagnosis is important to distinguish benign from malignant causes of biliary strictures, but existing tissue acquisition methods lack adequate accuracy.

Bile duct brushing during ERCP can be used to diagnose biliary malignancy; however, it has limited sensitivity.[3,4]

It has been reported that a serum carbohydrate antigen 19-9 level of more than 100 U/mL has a sensitivity of 53% and a specificity of 92% for the diagnosis of malignancy in biliary strictures[29]; however, it cannot provide a definitive diagnosis. Moreover, in patients who are negative for Lewis antigen elevated carbohydrate antigen 19-9 levels do not develop.[30]

These limitations underscore the need for a reliable modality to diagnose malignant biliary strictures. Although EUS-FNA has been used to provide tissue diagnosis in biliary strictures, there has been wide variability in the reported sensitivity of EUS-FNA in malignant biliary strictures. In this meta-analysis of 20 studies, we demonstrated that EUS-FNA performs well as a diagnostic test for malignant biliary strictures with an area under receiving-operating characteristic curve of 0.97. Such proximity of the area under the curve to 1 is a strong indicator of the high diagnostic accuracy of EUS-FNA.

In our meta-analysis, EUS-FNA has a pooled sensitivity of 80% and a specificity of 97% to diagnose malignant

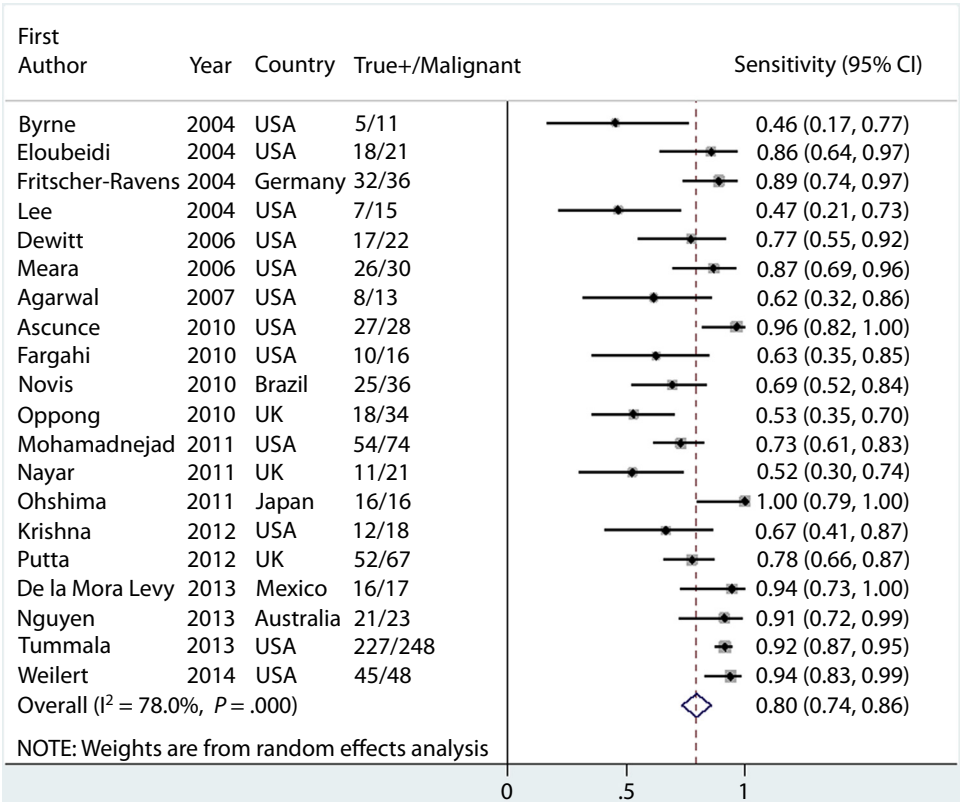

Figure 3. Forest plot showing pooled sensitivity for EUS-FNA in malignant biliary strictures. *CI*, confidence interval.

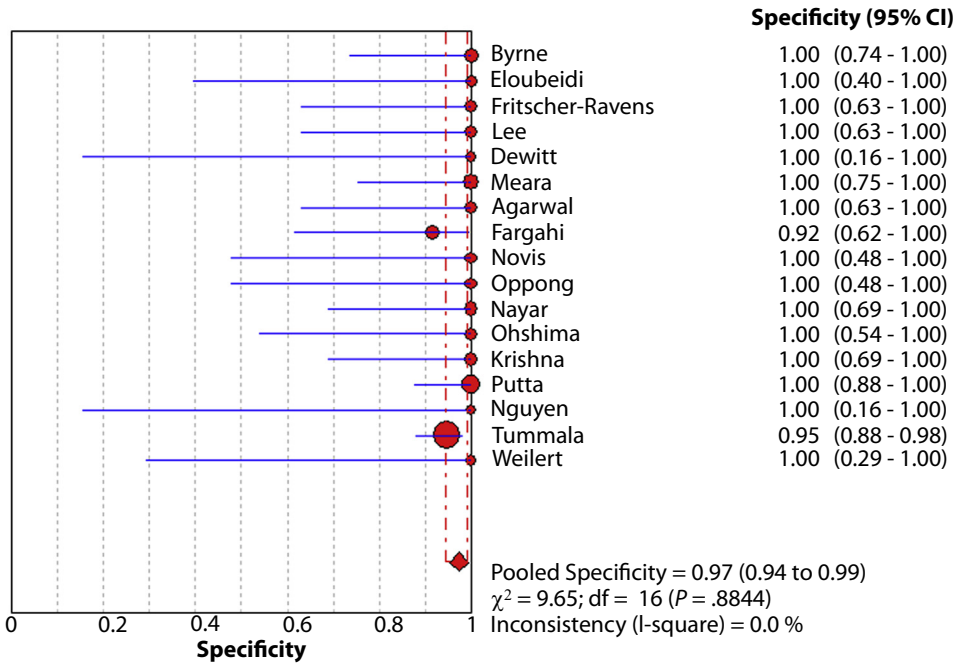

Figure 4. Forest plot showing pooled specificity for EUS-guided FNA in malignant biliary strictures. In the specificity analysis 17 studies were included, because 3 studies did not contain true negative case. *CI*, confidence interval.

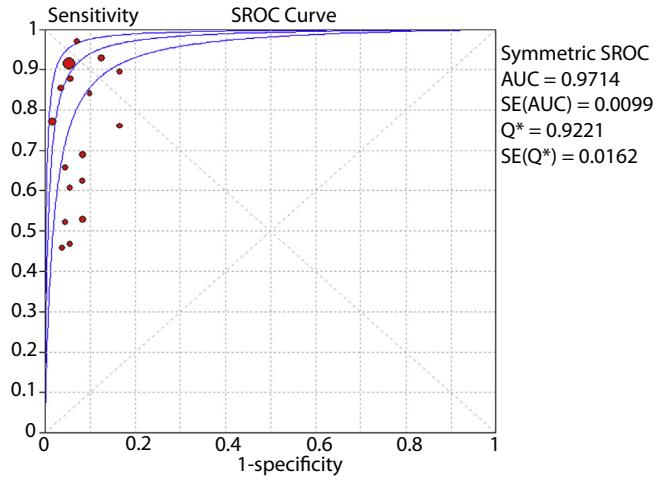

Figure 5. The summary receiver-operating characteristic (SROC) curve of EUS, with 95% confidence interval for the diagnostic yield of EUS-guided FNA in malignant biliary strictures. *AUC*, area under the curve; Q*, the point at which sensitivity and specificity are equal; *SE*, standard error.

biliary stricture. This is well above the reported sensitivity of 33% to 58% for bile duct brushing during ERCP.[13,31-36]

A positive likelihood ratio greater than 10 provides strong evidence to rule in a diagnosis, whereas a negative likelihood ratio less than 0.1 almost rules out a diagnosis. According to our analysis, the positive and negative likelihood ratios are also favorable. The positive likelihood ratio of 12.35 essentially rules in malignancy; the negative likelihood ratio of 0.26 is noteworthy, but it cannot reliably exclude malignancy.

We performed several sensitivity analyses. The consistent results observed across these analyses further validate the findings of this study. We also assessed the diagnostic yield of EUS-FNA in bile duct cancer after excluding extrinsic compression from the pancreatic head cancer. We observed that a pooled sensitivity of 79% in this subgroup was the same as the sensitivity calculated in all 20 studies together.

We also compared the diagnostic yield of EUS-FNA in distal and proximal biliary strictures. The distal portion of the common bile duct lies very close to duodenal wall and is easily visualized on EUS, whereas the proximal perihilar bile ducts course closer to the liver away from the duodenal wall.[20] Therefore, we expect that performance of EUS-FNA for tissue acquisition of the distal portion of extrahepatic bile duct is more favorable than proximal biliary tree.

In this meta-analysis, we observed that EUS-FNA has a sensitivity of 76% in proximal biliary strictures, whereas it has a sensitivity of 83% in distal biliary strictures. However, the pooled diagnostic odds ratio of EUS-FNA was 47.78 for proximal biliary strictures, and it was 33.88 with a wide confidence interval for distal biliary strictures. Such a discrepancy might be related to the low number of studies (eg, 4 studies) that specifically looked for EUS-FNA in distal biliary strictures. The impact of location of biliary stricture on the diagnostic accuracy of EUS-FNA should be further assessed in future studies.

In this study, the specificity of EUS-FNA was 97% for diagnosing malignancy. This is in line with the false-positive rate of 1%[37] and 7%[38] for EUS-FNA reported in previous studies.

In this meta-analysis, we observed asymmetry in the Deeks' funnel plot. The asymmetric funnel plot may be due to publication bias or other factors such as variations in test procedure, reference standards, and study design quality.[39] Publication bias raises concern about the possible existence of studies not included in the meta-analysis. Generally, larger studies are less likely to remain unpublished or ignored,[40] and smaller studies of lower quality are at higher risk of remaining unpublished. We performed several sensitivity analyses and observed that the sample sizes or quality scores of the studies did not decrease the calculated diagnostic accuracy of EUS-FNA in malignant biliary strictures.

It is also reported that the fewer literature databases that were searched increases the chance of publication bias.[39] We performed a comprehensive literature search of several databases and also a conducted manual search for major gastroenterology conferences to minimize the possibility of publication bias.

A meta-analysis published in 2011 evaluated the utility of EUS-FNA in bile duct and gallbladder cancer.[41] However, that study combined the studies on both gallbladder and bile duct cancer and did not specifically assess the performance of EUS-FNA in bile duct strictures. Furthermore, several large recent studies on this subject were not included in that meta-analysis.[18-28]

Another recent meta-analysis assessed the performance of EUS-FNA in biliary stricture.[42] However, only 6 studies were included in that meta-analysis. In the current study, we included 20 studies involving 957 patients.

Single-operator cholangioscopy is being increasingly used in indeterminate biliary strictures. Cholangioscopy-guided target biopsy has a sensitivity of 77%,[43] which is comparable to the pooled sensitivity of 80% for EUS-FNA observed in this meta-analysis.

Cholangioscopy may be associated with higher rates of adverse events than ERCP alone.[44] Adverse events have been reported in up to 7% of the patients undergoing cholangioscopy.[44] However, we observed a 1% rate of overall adverse events and only a 0.3% rate of major adverse events for EUS-FNA in this meta-analysis.

The cost of the procedure should also be taken into account. It has been reported that performing EUS-FNA in indeterminate biliary strictures prevented the high cost and adverse events of cholangioscopy in 60% of the patients and resulted in a cost saving of US$110,000 over 2 years at a single center.[26]

We thus propose a strategy that uses cholangioscopy in patients with indeterminate biliary stricture after EUS-FNA findings are inconclusive.[45]

Probe-based confocal laser endomicroscopy is a new and promising method of intraductal imaging of biliary strictures. A recent multicenter study reported a sensitivity of 89% for probe-based confocal laser endomicroscopy.[46] However, this method may misdiagnose some inflammatory strictures as malignant lesion, and it has a reported specificity of 71%.[46,47] The role of probe-based confocal laser endomicroscopy in the evaluation of indeterminate biliary strictures remains to be elucidated and will require further validation studies.

Seeding of tumor cells along the needle track has been well described in percutaneous needle biopsy sampling.[48] However, needle-track seeding appears to be a rare adverse event after EUS-FNA.[49] This could be explained by the small size of EUS-FNA needles and shorter needle track compared with the percutaneous approach.[49] To our knowledge, there have only been 3 reported cases of possible needle-track seeding associated with EUS-FNA.[50-52]

Needle-track seeding is less concerning in distal biliary malignancy in which the needle track of transduodenal EUS-FNA is fully resected during pancreaticoduodenectomy.[53] However, some authors discourage performing EUS-FNA in perihilar cholangiocarcinoma.[53] In addition, EUS-FNA is considered an absolute contraindication under the only currently approved liver transplantation protocol for perihilar cholangiocarcinoma in the United States.[47]

Contrary to this notion, a recent large single-center study reported that EUS-FNA does not adversely affect overall survival or progression-free survival in cholangiocarcinoma.[49]

In summary, this meta-analysis summarizes the available evidence for the performance of EUS-FNA in indeterminate biliary strictures. This modality has an excellent specificity of 97%, a good sensitivity of 80%, and a low adverse event rate in the diagnosis of malignant biliary strictures. EUS-FNA clearly outperforms brushing during ERCP for tissue acquisition in biliary strictures.[28] Given the good sensitivity of EUS-FNA and its low rate of adverse events, it is preferred over brushing for tissue diagnosis of biliary stricture. However, a negative test result on EUS-FNA cannot ensure the lack of malignancy, and the patient will require close surveillance and repeat sampling with other diagnostic modalities.

Further studies are needed to compare EUS-FNA with emerging methods including cholangioscopy-guided biopsy and laser endomicroscopy.

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SUPPLEMENTARY TABLE 1. Sensitivity analysis using the jackknife approach, where each study is excluded at the time to test sensitivity and specificity of EUS-FNA in malignant biliary stricture

Omitted Study: First Author, Year of Publication	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
All studies included	79.6 (73.5–85.6)	97.0 (94.0–99.0)
Byrne, 2004	79.1 (70.3-86.3)	98.0 (93.3-100.0)
Eloubeidi, 2004	78.2 (68.1-84.9)	98.4 (93.6-100.0)
Fritscher-Ravens, 2004	76.2 (75.6–76.8)	96.9 (96.8–96.9)
Lee, 2004	75.2 (74.6–75.8)	96.8 (96.7–96.8)
Dewitt, 2006	78.1 (76.5–82.7)	98.1 (96.7–99.8)
Meara, 2006	77.2 (67.3–85.8)	98.1 (93.1–100.0)
Agarwal, 2007	79.2 (69.2–86.3)	98.1 (93.1–100.0)
Ascunce, 2010	79.1 (78.5–84.7)	97.1 (95.7–99.8)
Fargahi, 2010	78.5 (74.9–76.1)	96.9 (94.8–99.9)
Novis, 2010	75.3 (74.7–75.9)	96.8 (94.8–99.9)
Oppong, 2010	75.3 (74.7–75.9)	96.8 (92.8–100.0)
Mohamadnejad, 2011	77.2 (67.3–87.3)	98.1 (93.1–100.0)
Nayar, 2011	79.1 (78.5–84.7)	96.1 (95.7–99.8)
Ohshima, 2011	78.5 (74.9–76.1)	96.6 (95.8–99.9)
Krishna, 2012	75.3 (74.7–75.9)	96.8 (94.8–99.9)
Putta, 2012	75.3 (74.7–75.9)	95.8 (91.1–98.9)
De la Mora Levy, 2013	79.2 (69.2–86.3)	98.1 (93.1–100.0)
Nguyen, 2013	79.1 (78.5–84.7)	97.1 (95.7–99.8)
Tummala, 2013	78.5 (74.9–76.1)	96.9 (91.8–98.9)
Weilert, 2014	75.3 (74.7–75.9)	96.8 (93.8–100.0)