—Review Article—

Endoscopic retrograde cholangiopancreatography versus endoscopic ultrasound for tissue diagnosis of malignant biliary stricture: Systematic review and meta-analysis

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ABSTRACT

Background and Aims: There are no systematic reviews comparing the use of endoscopic retrograde cholangiopancreatography (ERCP)-based brush cytology and forceps biopsy and endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) for the diagnosis of malignant biliary stricture; so in this revision, we will compare ERCP against EUS-FNA for tissue diagnosis of malignant biliary stricture. **Design:** A systematic review was conducted of comparative studies (prospective or retrospective) analyzing EUS and ERCP for tissue diagnosis of malignant biliary stricture. **Materials and Methods:** The databases Medline, EMBASE, Cochrane, LILACS, CINAHL, and Scopus were searched for studies dated previous to November 2014. We identified three prospective studies comparing EUS-FNA and ERCP for the diagnosis of malignant biliary stricture and five prospective studies comparing EUS-FNA with the same diagnosis of the other three studies. All patients were subjected to the same gold standard method. We calculated study variables (sensitivity, specificity, prevalence, positive and negative predictive values, and accuracy) and performed a meta-analysis using the Review Manager (RevMan) 5.3 software. **Results:** A total of 294 patients were included in the analysis. The pretest probability for malignant biliary stricture was 76.66%. The mean sensitivities of ERCP and EUS-FNA for tissue diagnosis of malignant biliary stricture were 49% and 75%, respectively; the specificities were 96.33% and 100%, respectively. The posttest probabilities positive predictive value (98.33% and 100%, respectively) and negative predictive value (34% and 47%, respectively) were determined. The accuracies were 60.66% and 79%, respectively. **Conclusion:** We found that EUS-FNA was superior to ERCP with brush cytology and forceps biopsy for diagnosing malignant biliary strictures. However, a negative EUS-FNA or ERCP test may not exclude malignant biliary stricture because both have low negative posttest probabilities.

Key words: Bile duct neoplasm, cholangiocarcinoma, endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), Klatskin tumors

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INTRODUCTION

Biliary strictures are always challenges for accurate diagnosis and management. At the onset of symptoms, the disease is typically already in an advanced stage.[1-4] Malignant strictures of the biliary tract are commonly caused by pancreatic cancer, periampullary cancer, or cholangiocarcinoma. Cholangiocarcinoma is the most common tumor of the biliary tract. The incidence varies based on geography, and the highest rates are seen in Southeast Asia.[5-7]

In the United States, approximately 5,000 cases are diagnosed annually.[8-10]

Cholangiocarcinomas can be classified using anatomical location as intrahepatic, perihilar (proximal), and extrahepatic (distal) cholangiocarcinomas.[11,12]

For unknown reasons, in recent years, the incidence and mortality of extrahepatic cholangiocarcinomas has decreased while that of intrahepatic cholangiocarcinomas has increased.[3,13,14]

Perihilar cholangiocarcinoma, also known as Klatskin tumor, involving the bifurcation of the hepatic duct is the most common, accounting for about 60%-80% of cholangiocarcinomas. Intrahepatic cholangiocarcinomas are the least common.[15-17]

Factors considered for therapeutic programming of biliary stricture include extension of the tumor, tumor anatomy, and results of histopathological study.

Noninvasive diagnosis of an indeterminate biliary stricture can be accomplished using serum tumor markers, radiological imaging such as ultrasound scan (USS), magnetic resonance (MR), positron emission tomography (PET), and computed tomography (CT) cholangiography, or endoscopic methods such as endoscopic retrograde cholangiopancreathography, endoscopic ultrasound (EUS), and cholangioscopy.[1,18-21]

The most common methods of obtaining tissue samples for diagnosis are endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology and/or forceps biopsy and endoscopic ultrasound with fine-needle aspiration (FNA).

In the literature, results obtained using endoscopic brush cytology and biopsy are very heterogeneous. Brush cytology sensitivity and specificity varies from 26% to 72%, and for biopsy it ranges between 15% and 100%. Results of EUS-FNA are heterogeneous as well, varying in sensitivity from 27% to 83%.

Patients typically have biliary strictures of indeterminate etiology. If they are good candidates for surgery, the use of EUS could avoid ERCP. However, if they are not good candidates, ERCP could be employed to treat jaundice and to confirm diagnosis.

Because the diagnostic yield of EUS and ERCP is variable for indeterminate malignant biliary stricture and because there are uncertainties about the best method, we have decided to perform this review to determine which one is superior. To our knowledge, no formal quantitative review of the literature has been published comparing the diagnostic performances of ERCP and EUS for tissue diagnostics of suspected malignant biliary strictures. In this revision, we will compare ERCP against EUS-FNA for tissue diagnosis of malignant biliary stricture.

OBJECTIVES

The aim of this study was to perform a structured meta-analysis of all eligible studies to compare the tissue diagnostic abilities of ERCP and EUS in cases of suspected malignant biliary stricture. To address the diagnoses of indeterminate malignant biliary strictures, clinical trials and observational studies were searched.

MATERIALS AND METHODS

Protocol and registration

This systematic review of the literature was conducted in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations.[22] The review was registered in the PROSPERO international database under number CRD42014015411.[23]

Eligibility criteria

a. *Types of studies* — Clinical trials and observational studies were searched and targeted for a posterior selection process.
b. *Types of participants* — We chose studies with patients who had indeterminate malignant biliary strictures and with similar population characteristics (age, sex, abnormal liver function tests, and evidence of biliary obstruction).

c. *Types of intervention* — We chose trials that used either ERCP or EUS-FNA in diagnostics. There were no restrictions regarding the modality of diagnosis in each.
d. *Types of outcome measures* — The main outcomes were accuracy, sensitivity, specificity, positive predictive value, and negative predictive value.

Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied as far as language was concerned. This search was applied to Medline.[24] In EMBASE, a resumed strategy was needed.[25] The Cochrane, LILACS (via BVS), Scopus, and CINAHL (via EBSCO), databases were also reviewed.[26,27] The last search was performed on November 10, 2014.

Search

The following search strategy was used in the Medline database.

Cholangiocarcinoma or cholangiocarcinomas or cholangiocellular carcinoma or bile duct neoplasm or neoplasm, bile duct or neoplasms, bile duct or bile duct cancer or bile duct cancers or cancer, Bile duct or cancers, bile duct or cancer of the bile duct or cancer of bile duct or Klatskin or Klatskin tumor or Klatskin tumors and endosonography or endosonographies or endoscopy, echo or echo endoscopies or endoscopies, echo or ultrasonic endoscopy or echo-endoscopy or echo endoscopy or echo-endoscopies or endoscopy, ultrasonic or endoscopies, ultrasonic or ultrasonic endoscopies or ultrasonography, endoscopic or endoscopic ultrasonography or endoscopic ultrasonographies or ultrasonographies, endoscopic.

In the EMBASE, Cochrane, LILACS, Scopus, and CINAHL databases, the search was "bile duct neoplasm and ERCP and endoscopic ultrasound."

Study selection

Eligibility assessment and selection of screened records were performed independently in an unblinded standardized manner by two reviewers. Disagreements between the reviewers were resolved by a consensus.

To summarize the study selection processes, an adapted PRISMA flow diagram was used.[22]

Data collection process

The method of data extraction from each included study consisted of collecting data on information sheets after reading the paper. A QUADAS-based checklist was used and the data were analyzed using Openepi and Catmaker tables.[28-30] One author extracted data from included studies and another checked the extracted data. Disagreements were resolved by discussion between the authors.

Data items

Population characteristics (patients included in the analysis with suspected malignant biliary strictures and clinical indications for the test), study design, test methods, gold standard used, EUS-FNA versus gold standard, and ERCP versus gold standard were obtained from the published trials. The study populations were first classified according to the suspect lesion in the biliary tract, and then patients diagnosed with malignant lesions were considered to be true positives, whereas patients with benign lesions were considered to be negative.

Risk of bias in individual studies

To evaluate the risk of bias and applicability of primary diagnostic accuracy, we used the QUADAS-2 tool.[28] It consists of four key domains: Patient selection, index test, reference standard, and flow and timing, each assessed in terms of risk of bias. The first three domains are also assessed in terms of applicability. Signaling questions are included to assist in judgments about risk of bias [Table 2]. The principal four questions of QUADAS-2 are:

1. Did the study avoid inappropriate exclusion?
2. Could the conduct or interpretation of the index test have introduced bias?
3. Could the reference standard, its conduct, or its interpretation have introduced bias?
4. Could the patient flow have introduced bias? These questions were answered to evaluate the risk of bias in the studies.

Summary measures

The analyses of sensitivity, specificity, pretest probability, positive and negative predictive values, and accuracy of EUS-FNA and ERCP for detection of a malignant lesion were the primary outcome measures. These values were calculated from the data provided in the original papers. Also, averages and standard deviations (SDs) of the main outcomes were analyzed using Review Manager (RevMan) 5.3, obtained from the website of Cochrane Informatics and Knowledge Management Department. Averages and SDs were obtained using Microsoft Excel Software for Windows version 2013.[31,32]

Synthesis of results

Data entered (true positives, false positives, true negatives, and false negatives) were converted to percentage values and graphs by the RevMan software package.

Risk of bias across studies

Publication bias is the influence on what is likely to be published, among what is available to be published. A problematic and much discussed bias is the tendency of researchers and editors to focus on positive results of trials, and actions such as deleting inconclusive results leads to a bias that increases the number of positive results.

Attention to selection bias, performance, detection, and confusion, for example, triggers a targeted and focused analysis.

Additional analyses

A common receiver operating characteristic (ROC) curve was used to facilitate interpretation of the results.

RESULTS

Study selection

One thousand and nine (1,009) studies were screened and assessed for eligibility after the titles and abstracts were read. Of these, 951 were excluded because they were not related to our objective. Of the remaining 58, 50 were excluded. A total of eight studies were included for qualitative and quantitative analyses. This process is summarized in Figure 1.

Study characteristics

The important characteristics of the selected studies are summarized in Table 1. These values were extracted through a careful reading of included papers. The design, conduct, and gold standard analysis of these studies were similar. The main objective of these studies was evaluating the performance of EUS-FNA and ERCP for the detection of malignant biliary stricture.

Risk of bias within studies

Using QUADAS-2, we found that most studies did not impose bias [Table 2]. We noted that all the studies followed the same pattern of exclusion, with similar results, except for the one by Ohshima *et al.*, which was the only study with 100% specificity and sensitivity.

The gold standard does not introduce bias in any study, and all trials were considered to have the same gold standard, histopathology (surgery or the index test), and follow-up.

There was no introduction of bias in terms of the selection of patients but there were differences in the size of the suspect lesions, which may have facilitated the diagnosis. For example, Ohshima *et al.*, presented the best results, but also had the highest average lesion size.

The greatest bias in this review is in the location of the lesion, as only Weilert *et al.*, Ohshima *et al.*, Rosch *et al.*, and Eloubedi *et al.* did not refer lesions location. Nayar *et al.*, DeWitt *et al.*, and Fritscher-Ravens *et al.* selected proximal lesions while Novis *et al.* selected distal lesions.

Results of individual studies

We assessed pretest probability, sensitivity, specificity, positive predictive value, negative predictive values, and accuracy. During our evaluation, we found that the specificity and positive predictive values of both tests were excellent.

We noted that EUS-FNA appeared to be more sensitive than ERCP except in the study of Rosch *et al.* where it was the same. Both Rosch *et al.* and Nayar *et al.* showed no significant sensitivity for the diagnosis of indeterminate malignant biliary stricture using EUS-FNA.

Unfortunately, most of the studies showed low negative predictive values; the notable exceptions were Ohshima *et al.* and Fritscher-Ravens *et al.* who reported negative predictive values of 100% and 90%, respectively. All reports had pretest probability superiors higher than up to 50%.

Synthesis of results

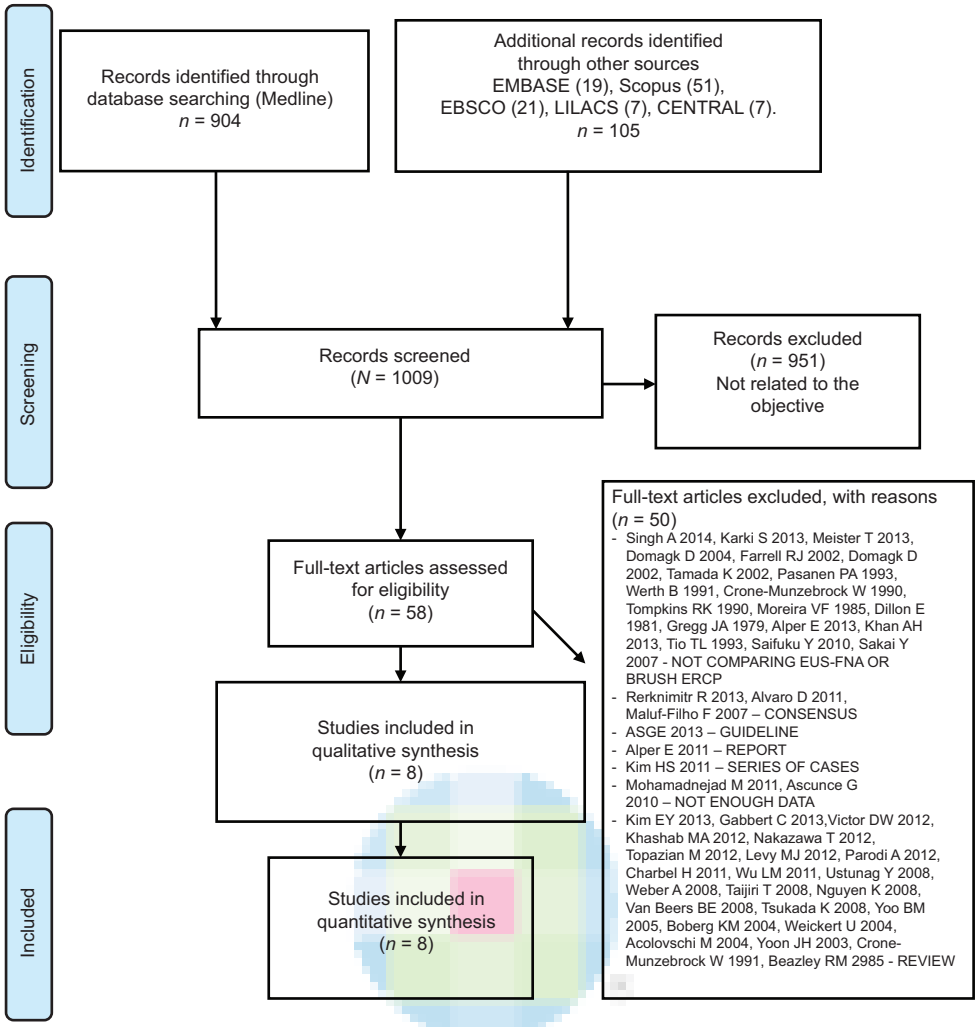
Analyzing the results of Table 3, we found that sensitivity had a value of around 50% for ERCP, showing that EUS-FNA was more sensitive. In addition, EUS-FNA was more accurate, specific, and had higher positive predictive values but ERCP had low negative predictive values.

The accuracies, sensitivities, specificities, prevalences, positive predictive values, and negative predictive values in EUS-FNA are reported in Table 4, showing that it had specificities of 100% as well as positive predictive values of 100% in all the relevant studies. In addition, the average sensitivity was 75% and the average accuracy was greater than 75%. As with ERCP,

Table 1. Characteristics of the studies

Study	Study design	Location	No. of patients included in the analysis	Median age (minimum-maximum)	Inclusion criteria	Lesion size	Intervention	Gold standard	Final diagnosis
Weilert 2014	Prospective Single-blinded	Biliary	51	67 (42-88)	Jaundice or elevated liver function test with a cholestatic pattern and evidence of biliary strictural obstruction or mass on preprocedure image	NA	EUS-FNA (22-25-gauge needle) + ERCP (biliary brush cytologic and intraductal forceps biopsies)	Surgery Findings of definite malignancy on EUS-FNA or ERCP Long-term follow-up	Malignant: 48 Pancreatic CA: 34 Gallbladder CA: 1 CCA: 13 Benign: 3
Nayar 2011	Retrospective	Proximal	32	66 (47-87)	Abnormal liver function tests and evidence of biliary strictural obstruction or mass on preprocedure image	3.18 cm (1-7 cm)	EUS-FNA (22-gauge needle)	Surgical pathology Results of EUS-FNA Follow up	Malignant: 24 CCA: 21 Gallbladder CA: 1 Hepatocellular CA: 1 Benign: 8
Ohshima 2011	Retrospective	Biliary	22	71.5 (53-79)	Suspect malignant biliary stricture after negative ERCP-Brush/forceps	23.5 mm (7-74 mm)	EUS-FNA (19-22-gauge needle, 19- 25-gauge needle)	Surgery Histology Follow up	Malignant: 16 CCA: 13 Squamous cell CA: 2 Undifferentiated CA: 1 Benign: 6
Novis 2010	Prospective	Distal	46	56	Distal biliary obstruction	NA	EUS-FNA (22-gauge needle) + ERCP (biliary brush cytologic)	Surgery Histology Follow-up	Malignant: 37 Pancreatic: 26 Biliary: 11 CBD: 8 Hilar: 3 Benign: 9
DeWitt 2005	Retrospective cohort	Proximal	24	68 (37-87)	ERCP with brush cytologic and/or fórceps biopsy either unsuccessful or pathologically interpreted as nondiagnostic or negative for malignancy	19 mm (5-53 mm)	EUS-FNA (22-gauge needle)	Surgical pathology Results of EUS-FNA Follow-up	Malignant: 17 CCA: 15 Lymphoma: 2 Benign: 7
Rosch 2004	Prospective	Biliary	50	62.1	Indeterminate biliary stricture or a mass in the head of pancreas	NA	EUS-FNA (22-gauge needle) + ERCP (intraductal forceps biopsies, conventional biliary brush cytologic, and spiral suction)	Surgery Other biopsy result Follow-up	Malignant: 28 Pancreatic: 16 Biliary: 12 (Distal: 8/Proximal: 4) Benign: 22
Eloubeidi 2004	Prospective	Biliary	25	67	Suspect cholangiocarcinoma based on clinical history, and imaging studies including follow-up	19 mm (11-35) x 16 mm (10-22)	EUS-FNA(22-gauge needle)	Surgery Follow-up	Proximal: 15 Distal: 10 Malignant: 18 (8 Klatskin) Benign: 7
Fritscher-Ravens 2004	Prospective	Proximal	44	59 (37-74)	High index of clinical suspicion based on imaging methods; biopsy or cytology taken during ERCP did not obtain material that was diagnostic malignant; and patient had been fit for hepatic resection	No significant differences in lesion size	EUS-FNA (22-gauge needle)	Surgery Autopsy Follow-up	Malignant: 31 CCA: 26 Benign: 12 Inadequate material: 1

Label: (minimum-maximum), NA: Not available, EUS-FNA: Endoscopic ultrasound-fine-needle aspiration, ERCP: Endoscopic retrograde cholangiopancreatography, CCA: Cholangiocarcinoma, CBD: Common biliary duct, CA: Carcinoma



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement.

Figure 1. PRISMA flow diagram

EUS-FNA had low negative predictive values, with the exception of Ohshima *et al.* and Ravens Fritscher *et al.*

Tables 5 and 6 show the sensitivities and specificities of EUS-FNA and ERCP.

The sensitivity of EUS-FNA ranged between 46% and 100%, averaging 75% while that of ERCP ranged between 46% and 50%, averaging 49%. Specificity of EUS-FNA was 100% in all studies while that of ERCP ranged from 89% to 100%, averaging 96%.

Table 7 shows a comparison between the average and variance of diagnostic variables.

In diagnosing suspected malignant biliary stricture, the sensitivity of EUS-FNA was superior to ERCP, averaging 75% (SD, 19.87) versus 49% (SD, 2.64). Its specificity was slightly superior, averaging 100% (SD, 0) versus 96.33% (SD, 6.35). Its mean positive predictive value was also superior to that of ERCP, averaging 100% (SD, 0) versus 98.33% (SD 2.22). Likewise, its mean negative predictive value was higher, averaging 47% (SD, 14.73) versus 34% (SD, 24.63). Finally, the aggregated accuracy of EUS-FNA was higher, averaging 79% (SD, 13.07) versus 60.66% (SD, 8.62).

Risk of bias across studies

The risks of bias were minimal because the articles followed the same patterns. The greatest bias was related to the lesion size and secondarily to the lesion location. The size of the trials varied, facilitating the chance of suitable material for pathological studies, which could introduce bias.

Table 2. QUADAS-2 questions and answers for the included studies

QUADAS-2	Weilert 2014	Novis 2010	Rosch 2004	Nayar 2011	Ohshima 2011	DeWitt 2005	Eloubeidi 2004	Fritscher-Ravens 2004
Was a consecutive or random sample of patients enrolled?	YES	YES	YES	YES	YES	YES	YES	YES
Was a case-control design avoided?	YES	YES	YES	YES	YES	YES	YES	YES
Did the study avoid inappropriate exclusions?	YES	YES	YES	YES	YES	YES	YES	YES
Could the selection of patients have introduced bias?	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
Are there concerns that the included patients do not match the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Were the index test results interpreted without knowledge of the results of the reference standard?	YES	YES	YES	YES	YES	YES	YES	YES
If a threshold was used, was it prespecified?	YES	YES	YES	YES	YES	YES	YES	YES
Could the conduct or interpretation of the index test have introduced bias?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Is the reference standard likely to correctly classify the target condition?	YES	YES	YES	YES	YES	YES	YES	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES	YES	YES	YES	YES	YES	YES	YES
Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Are there concerns that the target condition as defined by the reference standard does not match the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Was there an appropriate interval between index test(s) and reference standard?	YES	YES	NO	YES	NO	NO	NO	YES
Did all patients receive a reference standard?	YES	YES	YES	YES	YES	YES	YES	YES
Did all patients receive the same reference standard?	YES	YES	YES	YES	YES	YES	YES	YES
Were all patients included in the analysis?	YES	YES	YES	YES	YES	YES	YES	YES
Could the patient flow have introduced bias?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Table 3. Performance of ERCP compared to EUS-FNA for indeterminate biliary stricture

ERCP/EUS-FNA	Intervention	Pretest probability (%)	Sensitivity (%)	Especificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Weilert 2014	ERCP	94	50	50	100	11	53
	EUS-FNA		94	100	100	50	94
Novis 2010	ERCP	80	49	89	95	31	59
	EUS-FNA		68	100	100	31	73
Rosch 2004	ERCP	56	46	100	100	60	70
	EUS-FNA		46	100	100	60	70

Label: PPV: Positive predictive value, NPV: Negative predictive value, ERCP: Endoscopic retrograde cholangiopancreatography, EUS-FNA: Endoscopic ultrasound-fine-needle aspiration

Table 4. Performance of EUS-FNA for indeterminate malignant biliary stricture

EUS-FNA	Pretest probability (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Nayar 2011	54	52	100	100	54	59
Ohshima 2011	50	100	100	100	100	100
DeWitt 2005	96	77	100	100	29	83
Eloubeidi 2004	84	86	100	100	57	88
Fritscher-Ravens 2004	72	89	100	100	90	91
Weilert 2014	94	94	100	100	50	94
Novis 2010	80	68	100	100	31	73
Rosch 2004	56	46	100	100	60	70

Label: EUS-FNA: Endoscopic ultrasound-fine-needle aspiration, PPV: Positive predictive value, NPV: Negative predictive value

Additional analyses

The ROC curve comparing EUS-FNA and ERCP (brush cytology and forceps biopsy) are shown in Figure 2.

Figure 2 shows the ROC curve in which the best sensitivity and specificity are shown for both diagnostic arms. The EUS-FNA sensitivity and specificity were

87% and 90%, respectively, whereas for ERCP they were 75% and 81%, respectively.

Using Medcalc statistical software, we calculated the positive posttest probability and the accuracy of both methods, which for EUS-FNA were 96.5% and 87.7%, respectively. For ERCP, the values were 92.5% and 74.4%, respectively.[33]

A larger area below the line is seen for EUS-FNA; therefore, we conclude that it is a better method than ERCP for diagnosing suspected malignant biliary stricture.

DISCUSSION

Summary of evidence

EUS has an important role in the evaluation of patients with indeterminate biliary strictures and has advantages over ERCP because it has fewer complications, can identify adjacent structures, and can identify secondary causes of stenosis involving lymph nodes or neoplasms.

This review shows that EUS-FNA is a better method than ERCP for diagnosing suspected malignant biliary strictures. However, this study did not consider the site of lesion; it included studies of both distal and proximal lesions. Some authors have shown better results using EUS-FNA in distal lesions and ERCP in proximal lesions, primarily taking into account the type of the lesion.[34-37] Small lesions (<10 mm) are more difficult to sample using EUS-FNA and when the lesions present with wall thickening, this method has very low sensitivity; so the use of ERCP and cholangioscopy are preferable. In larger lesions, where masses and/or nodules appear, EUS-FNA is easier to perform and has better results.[9,38-40]

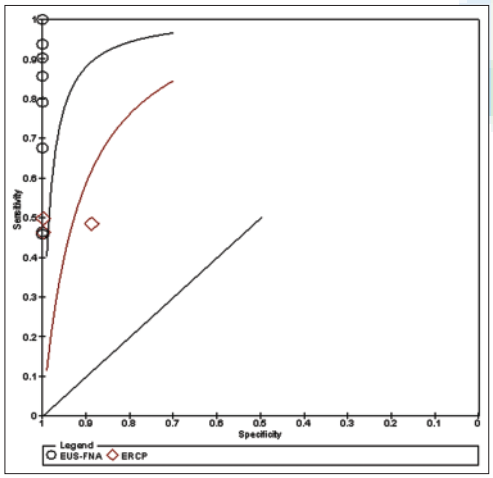


Figure 2. ROC curve

In cases of pancreatic tumors, EUS-FNA has high sensitivity and high specificity while ERCP has low sensitivity, ranging from 32% to 50%. In cases of papillary tumors, biopsy can be performed during duodenoscopy with high sensitivity and specificity.[15,41,42]

Our review shows that both methods have high specificities and high positive predictive values in diagnosing suspected biliary strictures, assuming that a positive test is trusted. Both have low negative predictive values; when any of the tests have negative values, the disease is not excluded. Therefore, if the first test is negative, combination with another method is the best way to diagnose a suspected malignant biliary stricture.

LIMITATIONS

The main limitation of this review is that none of the studies were randomized trials. Another limitation is that the negative predictive value is very high, which in the case of a negative test, means that one cannot exclude the disease.

CONCLUSIONS

This study demonstrates that EUS-FNA is better than ERCP for the detection of suspected malignant biliary

Table 5. Diagnosis of suspected malignant biliary stricture in EUS-FNA.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
DeWitt J 2005	19	0	5	1	0.79 [0.58, 0.93]	1.00 [0.03, 1.00]
Eloubeide MA 2004	18	0	3	4	0.86 [0.64, 0.97]	1.00 [0.40, 1.00]
Fritsher-Ravens A 2004	28	0	3	12	0.90 [0.74, 0.98]	1.00 [0.74, 1.00]
Nayar MK 2011	11	0	13	8	0.46 [0.26, 0,67]	1.00 [0.63, 1.00]
Novis M 2010	25	0	12	9	0.68 [0.50, 0.82]	1.00 [0.66, 1.00]
Ohshima Y 2011	16	0	0	16	1.00 [0.79, 1.00]	1.00 [0.79, 1.00]
Rosch T 2004	13	0	15	22	0.46 [0.28, 0.66]	1.00 [0.85, 1.00]
Weilert 2014	45	0	3	3	0.94 [0.83, 0.99]	1.00 [0.29, 1.00]

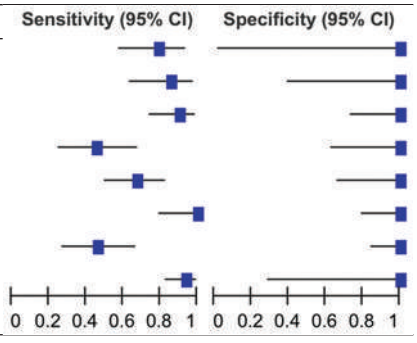


Table 6. Diagnosis of suspected malignant biliary stricture in ERCP

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Novis M 2010	18	1	19	8	0.49 [0.32, 0.66]	0.89 [0.52, 1.00]
Rosch T 2004	13	0	15	22	0.46 [0.28, 0.66]	1.00 [0.85, 1.00]
Weilert 2014	24	0	24	3	0.50 [0.35, 0.65]	1.00 [0.29, 1.00]

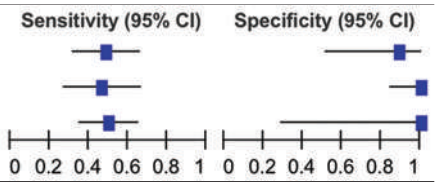


Table 7. Average and variance of diagnostic variables

Diagnostic variable	ERCP (%)	EUS-FNA (%)
Sensitivity	Average: 49	Average: 75
	SD: 2.64	SD: 19.87
Specificity	Average: 96.33	Average:100
	SD: 6.35	SD:0
Pretest Probability	Average: 76.66	
	SD: 19.2180	
Posttest probability		
Positive predictive value	Average: 98.33	Average:100
	SD: 2.22	SD: 0
Negative predictive value	Average: 34	Average: 47
	SD: 24.63	SD: 14.73
Accuracy	Average: 60.66	Average: 79
	SD: 8,62	SD: 13.07

Label: ERCP: Endoscopic retrograde cholangiopancreatography, EUS-FNA: Endoscopic ultrasound-fine-needle aspiration, SD: tandard deviation

stricture as it has superior sensitivity, specificity, positive posttest probability, and accuracy. A negative test using EUS-FNA or ERCP does not exclude a malignant biliary stricture because both have low negative posttest probabilities.

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Conflicts of interest

There are no conflicts of interest.

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