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Role of EUS-FNA Based Cytology in Diagnosis of Mucinous Pancreatic Cystic Lesions: A Systematic Review and Meta-analysis

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Abstract

Background—Preoperative diagnosis of malignancy in pancreatic cystic lesions (PCLs) remains challenging. Most non-mucinous cystic lesions (NMCLs) are benign, but mucinous cystic lesions (MCLs) are more likely to be premalignant or malignant.

Aim—The aim of this study was to assess the sensitivity, specificity, and positive and negative likelihood ratios (LRs) of EUS-FNA based cytology in differentiating MCLs from non-mucinous PCLs.

Methods—We conducted a comprehensive search of MEDLINE, SCOPUS, Cochrane, and "CINAHL Plus" databases to identify studies, in which the results of EUS-FNA based cytology of PCLs were compared with those of surgical biopsy or surgical excision histopathology. A DerSimonian-Laird random effect model was used to estimate the pooled sensitivity, specificity, and LRs, and a summary receiver-operating characteristic (SROC) curve was constructed.

Results—We included 376 patients from 11 distinct studies who underwent EUS-FNA based cytology and also had histopathological diagnosis. The pooled sensitivity and specificity in diagnosing MCLs were 0.63 (95% CI, 0.56–0.70) and 0.88 (95% CI, 0.83–0.93), respectively. The positive and negative LRs in diagnosing MCLs were 4.46 (95% CI, 1.21–16.43) and 0.46 (95% CI, 0.25–0.86), respectively. The area under the curve (AUC) was 0.89.

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Conclusion—EUS-FNA based cytology has overall low sensitivity but good specificity in differentiating MCLs from NMCLs. Further research is required to improve the overall sensitivity of EUS-FNA based cytology to diagnose MCLs while evaluating PCL.

Keywords

EUS; FNA; cytology; meta-analysis; pancreatic cyst lesions

INTRODUCTION

Pancreatic cystic lesions (PCLs) comprise a variety of pathologically different groups of lesions that usually share many common clinical features [1–4]. About 90% of PCLs are benign processes such as pseudocysts related to acute or chronic pancreatitis [4–6]. Pancreatic cystic neoplasms (PCNs) constitute 10–15% of all PCLs and less than 1% of all pancreatic neoplasms [3,7]. PCLs can be broadly classified into mucinous cystic lesions (MCLs) and non-mucinous cystic lesions (NMCLs). NMCLs include entities such as pseudocysts (PCs), serous cyst adenomas (SCAs), solid pseudopapillary tumors (SPTs), and pancreatic endocrine tumors (PETs). MCLs are classified into benign, borderline, and malignant tumors based on the degree of epithelial dysplasia [8–10]. Though MCLs can be benign, they are more likely to be premalignant or malignant; and early resection can provide excellent prognosis [3,11,12]. In the past decade, endoscopic ultrasound (EUS) has increasing used as a diagnostic tool for PCNs, as it can provide high-resolution images of PCLs and also enable EUS-guided FNA of pancreatic cystic fluid [13]. Despite advances in diagnostic modalities like EUS and cyst fluid analysis by EUS FNA, preoperative diagnosis of cystic lesions remains difficult.

MATERIAL AND METHODS

Search Strategy

We performed a systematic literature review by using the guidelines developed for conducting systematic review [14]. A comprehensive search of the MEDLINE (PubMed and Ovid from 1966 to October 2008), SCOPUS (consisting of Medline and Embase databases), Cochrane Database of Systemic Reviews, and “CINAHL Plus” databases, was conducted using four combinations of search terms: a) pancreatic cyst, endoscopy, FNA; b) EUS AND pancreas AND cyst; c) EUS, FNA, pancreatic cystic neoplasm; and d) pancreatic cystic tumors AND EUS. Our search was restricted to human subjects and English language studies.

Inclusion Criteria

Intervention—EUS-FNA of PCLs

Criterion standards—Final pathologic diagnosis by surgical biopsy or by histological examination of surgically resected specimen.

Population—Patients who had suspected PCLs based on ultrasound, CT scan, MRI, or EUS. Only patients who had PCLs were included in the study. Patients with pancreatic lesions with solid component were excluded from the study.

Study designs—Retrospective or prospective studies that compared the results of EUS-FNA based cytology with surgical biopsy or histology.

Outcomes—Results reported in sufficient details to construct a diagnostic 2 × 2 table (true positive, false positive, true negative, and false negative).

Exclusion Criteria

We excluded case reports and case series; studies in which EUS-FNA was done for solid pancreatic lesions, with or without cystic component; studies that included both cystic and solid pancreatic lesions; studies that included clinical follow up as a criterion standard without knowing the disease status based on surgical pathology; studies that included other FNA approaches, like CT guided FNA or ultrasound guided FNA, in reporting their final results; and studies that did not provide data sufficient to construct a diagnostic 2 × 2 table.

Histological Criteria

Based on WHO tumor classifications, we classified all PCLs as either MCLs or non-mucinous cystic lesions. All cystic lesions arising from intraductal papillary neoplasms also were classified as MCLs.

Data Abstraction

From the selected studies, two independent reviewers (N.T. and S.T.) extracted the following data onto standardized data forms (in Microsoft Excel™):

- Study characteristics: design, country, year of publication, setting, sample size, clinical context, and criterion standard
- Demographic characteristics: mean age, proportion of male and female, and prevalence of MCLs out of total PCLs
- Interventions: manufacture and operating frequencies of endoscope, gauge size, length, manufacturer of EUS-FNA needles, and cyto-pathological staining methods
- Outcomes: number of true positive, true negative, false positive, and false negative for MCLs of pancreas

Discrepancies were resolved by discussion and consensus with a third reviewer (S.G.).

Quality Criteria

Current quality assessment guidelines and tools focus on randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome to evaluate the quality of the clinical trials with control arm [15]. There is no consensus or criteria to evaluate the quality of the studies without a control arm [15]. Almost all of the studies focusing on the accuracy of EUS-FNA based cytology in PCLs are either retrospective or prospective

studies without control arm. Therefore, for this systematic review and meta-analysis we selected studies based on our pre-defined inclusion and exclusion criteria and completeness of data reporting in the studies.

Statistical Analysis

We constructed a 2 × 2 table for each study; for studies in which 0 counts occurred in study data, a continuity correction of 0.5 was added to every value in that study in order to calculate sensitivity and specificity. Based on the 2 × 2 table, we calculated the true positive, false positive, true negative, and false negative values and entered these into the statistical software package Meta-Disc version 1.4 (Meta-Disc, Unit of Clinical Biostatistics team of the Roman y Cajal Hospital, Madrid, Spain) [16]. We calculated the sensitivity, specificity, positive LR, negative LR, and diagnostic odds ratio (DOR: positive LR/negative LR) for each study and then pooled the results as per the DerSimonian-Liard random effects model [17]. Meta-Disc version 1.4 was used to generate Forest plots of sensitivity, specificity, positive LRs, and negative LRs. We performed subgroup analysis and calculated sensitivity, specificity, positive LRs and negative LRs for subgroup of four prospective studies.

Heterogeneity was assessed by using χ^2 statistics [18,19]. By using DerSimonian-Liard random effects model, we constructed a summary receiver operating characteristic curve (SROC) [17]. The area under the curve (AUC) was computed by numeric integration of the SROC equation by using the trapezoidal method [20]. A preferred test has an AUC close to 1, and a poor test has an AUC close to 0.5. We used the random effect meta-regression analysis and Moses-Shapiro-Litternberg method [21] to examine study design (prospective v/s retrospective), Single center versus multicenter, sex ratio, sample size, and EUS FNA needle size for the heterogeneity analysis. The results of the meta-regression model were expressed as relative diagnostic odds ratio (RDOR) of the corresponding covariate [21].

RESULTS

SYSTEMATIC REVIEW

Description of studies—Our study selection process is described in detail in Figure 1. Our initial search yielded 256 study titles and abstracts. Of these, 11 studies [22–32] met the predefined inclusion and exclusion criteria and were selected for meta-analysis. Ten studies were from USA, and 1 was from France [24]. Seven studies were retrospective [22,23,26,28–31] and 4 studies were prospective [24,25,27,32]. Altogether, the studies reported on 937 patients (361 male and 576 female). The mean age was 59 years. Of 937 total patients, EUS-FNA of PCLs had been performed on 788 patients and surgical biopsy or surgical resection had been performed on 446 patients. Of 446 patients with surgery, 70 patients underwent surgical resection based on clinical characteristics and EUS morphology without EUS-FNA and they were excluded from analysis. Similarly, of 788 patients with EUS-FNA, 412 patients did not receive a final diagnosis by surgical biopsy or resection and they were also excluded from analysis. This left 376 patients who received both a satisfactory EUS-FNA for cytological diagnosis and the gold standard comparison by either surgical histology or biopsy. The study characteristics of the included manuscripts are shown in Table 1. Seven [22,24,29–32] out of 11 studies further differentiated mucinous

cysts into mucinous cyst adenoma, mucinous adenocarcinoma and intra papillary mucinous neoplasia. Table 2 details the results of EUS-FNA and final histology for each mucinous cyst subtypes (MCAs, IPMNs, and Adenocarcinomas) in the 7 studies.

EUS-FNA Method—Most studies used 22-gauge needles (Wilson-Cook, Medical Inc, Winston-Salem, N.C.) [27,28,30–32], though some also used 19-gauge [25,27,31,32] (Wilson-Cook, Medical Inc, Winston-Salem, NC and Mediglobe, Tempe, AZ), 23-gauge [26] (Pentax 23-guage, 4-cm needle), and 25-gauge [27] needles (EchoTip; Wilson-Cook, Medical Inc, Winston-Salem, NC).

META-ANALYSIS

Diagnostic Accuracy—Figure 2 shows the Forest plots of sensitivity and specificity of EUS-FNA based cytology for the diagnosis of mucinous PCLs. Point estimates were plotted with 95% confidence intervals (CIs) for each cohort. The pooled sensitivity of EUS-FNA based cytology in diagnosing MCLs was 0.63 (95% CI, 0.56–0.70) and pooled specificity was 0.88 (95% CI, 0.83–0.93). The positive LR was 4.46 (95% CI, 1.21–16.43) and the negative LR was 0.46 (95% CI, 0.25–0.86) (Figure 3). The *P* value for χ^2 heterogeneity for all the pooled estimates was less than 0.05 suggesting heterogeneity amongst the studies. To explore heterogeneity, we performed a subgroup analysis of 4 prospective studies. In subgroup analysis of 4 prospective studies, the pooled sensitivity of EUS-FNA based cytology was 0.54 (95% CI, 0.45 to 0.62) and the pooled specificity was 0.92 (95% CI, 0.85 to 0.96) (Figure 4). Similarly the pooled positive LR was 8.22 (95% CI, 0.82 to 82.36) and the pooled negative LR was 0.47 (95% CI, 0.20 to 1.12) (Figure 5). The overall accuracy of EUS in a SROC plot for meta-analysis and subgroup analysis is shown in Figure 6. The symmetric curve shows a trade-off between sensitivity and specificity. The AUC was 0.89 for all 11 studies and was 0.99 for 4 prospective studies, indicating high test accuracy.

Among the 7 studies [22–24,29–32] that further differentiated mucinous cyst into MCAs, mucinous adenocarcinomas and IPMNs, EUS-FNAs were able to correctly diagnose 26 of 46 (56.52%) of MCAs, 23 of 23 (100%) of mucinous adenocarcinomas and 70 of 96 (72.91%) of IPMNs (Table 2).

We identified 13 potential sources of heterogeneity: (1) study design(prospective versus retrospective), (2) single center versus multi-center, (3) sample size, (4) sex ratio, (5) cyst location, (6) cyst size, (7) EUS-FNA needle size, (8) average needle pass, (9) amount of the cyst fluid aspirated, (10) presence or absence of the cytopathologist at time of cyst aspiration, (11) average time from aspiration of cyst fluid to preparation of slide, (12) type and total number of histological stains are used, and (13) experience of the cytopathologist. However, the 11 primary studies provided data sufficient to analyze heterogeneity for only 5 of the 13 identified sources: study design, single center versus multi-center, sample size, sex ratio, and EUS-FNA needle size. Meta-regression for study design, single center versus multi-center, sample size, and sex ratio did not show any statistical significant difference. Of 11 studies, 10 reported needle sizes for EUS-FNA. Meta-regression for needle size in these 10 studies did not show statistically significant difference. The outcomes of the regression analysis as RDOR are shown in Table 3.

DISCUSSION

EUS-FNA has a diagnostic advantage over other FNA methods, including CT-guided FNA and US-guided FNA, that historically have been relatively unsuccessful as pancreatic cysts can be very small and inaccessible [33–35]. This systematic review of EUS-FNA based cytology for patients who have PCLs found that EUS-FNA has good diagnostic accuracy, with an AUC of 0.89. Our meta-analysis showed EUS-FNA based cytology to have a pooled sensitivity of 63% (95% CI, 0.56–0.70) and a pooled specificity of 88% (95% CI, 0.83–0.93). The subgroup analysis of 4 prospective studies showed sensitivity 0.54 (95% CI, 0.45 to 0.62) and specificity 0.92 (95% CI, 0.85 to 0.96). In our study the positive and negative LRs were 4.93 (95% CI, 1.35–18.08) and 0.46 (95% CI, 0.27–0.80) respectively. Further, analysis of different mucinous cyst subtypes revealed EUS-FNA accurately diagnosed mucinous adenocarcinomas (100%) and IPMNs (72.91%) more frequently than it diagnosed MCAs (56.52%). The pooled sensitivity of 63% might be overestimated than the real sensitivity secondary to verification bias [36]. Verification bias occurs when out of all the patients who had diagnostic test only a subgroup of patient undergoes confirmatory test. Verification bias can be avoided by requiring everyone who enrolls in the study, to undergo confirmatory test (i.e. pancreatic cyst biopsy or surgical resection) irrespective of the positive or negative diagnostic test (i.e. EUS-FNA) result but this is not practical and ethical. It is reasonable to assume that patients with positive EUS-FNA based cytology were more likely to undergo confirmatory test than the patients with negative EUS-FNA based cytology raising the sensitivity of the diagnostic test. For the same reason the pooled specificity of 88% might be underestimated than the real specificity. Further calculations for the verification bias were not possible secondary to lack of adequate reporting in the included studies.

Major pitfalls in diagnosis of PCLs by EUS-FNA include a high frequency of insufficient aspirates and difficulty in differentiating pathological mucin from gastrointestinal contaminant secondary to a transgastric or transduodenal approach of EUS-FNA. Most studies have shown that rapid on-site evaluation (ROSE) by the cytopathologist can help to assess adequacy of sample and also improve diagnostic yield of the procedure. A recent study by Hikichi et al showed even when a cytopathologist is not available, rapid on-site evaluation by endosonographer is equally effective and helps to increase the diagnostic yield [37]. The presence of extra-cellular mucin or intracytoplasmic mucin within neoplastic cells aids in the diagnosis of mucinous neoplasms. Pathological mucin is grossly thicker and more viscid, and on air-dried Diff-Quick stained smears or ethanol fixed Papanicolaou stained smears, it appears more abundant than gastrointestinal contaminant does. If only liquid based preparations are mad, then mucus is very difficult to appreciate.

Frossard et al [24] prepared cell blocks and used special mucin stains like hematoxylin-eosin-saffron, periodic acid-Schiff, and Alcian blue, in addition to routine Diff-Quick stained smears. They used the ThinPrep 2000 processor (Cytyc Corporation, Marlborough, MA) to concentrate scant fluids to generate mono-layered cell populations with cleaner backgrounds and had the same pathologist analyze all smears and biopsies. In this study, 67 patients met our inclusion criteria, and for this subset of patients, the EUS-FNA based cytology had sensitivity and specificity of 100%; only 1 patient who had a MCA was

diagnosed as having an IPMN. In contrast, Attasaranya et al [30] prepared one air dried, modified Giemsa stained smear, and one alcohol fixed, Papanicolaou stained smear for on-site evaluation. Of the 48 aspirates taken 14 were hypocellular to make an FNA diagnosis. They did not perform any mucin stains on any specimens. In their subset of 34 patients, the EUS-FNA based cytology had sensitivity of 23% and a specificity of 71%. These conflicting results among these studies might suggest that presence of on-site cytopathologist, and a standardize protocol for smear stains combined with the use of special mucin stains and a ThinPrep 2000 processor can help to improve the diagnostic accuracy of EUS-FNA based cytology.

Our systematic review identified that current literature on diagnostic accuracy of EUS-FNA based cytology for PCLs is limited and heterogeneous. There is no randomized clinical trial focusing on this issue. In our meta-analysis, heterogeneity is probably caused by factors that were inadequately reported in the 11 primary studies and, therefore, cannot be explored. These factors include cyst size and location, volume of the aspirated cyst fluid, presence of a cytopathologist in the endoscopy suite during the procedure, time interval from the aspiration of cyst fluid to the preparation of pathological slides, the methods of staining, and experience of cyto-pathologist. Although we were not able to demonstrate needle size as a significant factor for heterogeneity due to lack of adequate data reporting, a recent study by Song et el clearly showed that for solid pancreatic lesions, EUS-FNA with 19 gauge needle had significantly higher diagnostic accuracy compared to 22 gauge needle (93.9 vs. 78.1, $p<0.05$)[37]. Also 19 gauge needle required less number of needle passages and aspirated significantly higher amount of cellular material [38].

In addition to cytology, cyst fluid analysis for tumor markers including CEA, CA 19-9, CA 72-4, CA 125, and molecular markers including *K-ras* mutations and loss of heterogeneity (LOH) was also performed in several studies [25,27,28]. Cooperative pancreatic cyst study reported that a cut off value of 192 for CEA has the greatest AUC (0.79) for differentiation of mucinous versus non-mucinous PCLs [25]. The study also reported that CEA has greater accuracy, in diagnosing MCLs, than EUS morphology or cytology [25]. However different studies reported different cut-off values for CEA analysis including 5, 148, 192, 300, 467, and 800 [25,32,38–41]. Based on 36 cyst fluid samples, Khalid *et al* reported that occurrence of *K-ras* mutations as a first hit had sensitivity of 91% and specificity of 86%, whereas presence of allelic loss (measured by LOH) after *K-ras* mutations had sensitivity of 91% and specificity of 93% respectively [27]. These studies show a promising role of CEA and molecular analysis in differentiating MCL from non-mucinous PCLs. CEA can be a very valuable tumor marker; however more research is needed to define clear cut-off values for CEA. Initial studies on molecular analyses of pancreatic cancer associated mutations of *K-ras* and other oncogenes/tumor-suppressor genes and expression of novel biomarkers are quite promising but more trials with larger sample sizes are needed in this direction.

In conclusion, based on the currently available English language literature, our meta-analysis reveals that EUS-FNA based cytology has overall low sensitivity but good specificity in differentiating mucinous from non-mucinous PCLs. Rapid on-site evaluation by a cytopathologist or an endosonographer, use of standardized techniques for smear staining, use of special mucin stains and use of the ThinPrep 2000 to provide a mono-

layered cell populations with cleaner backgrounds can help to increase diagnostic yield of EUS-FNA based cytology. Well designed randomized trials are needed to further explore the role of EUS-FNA based cytology in differentiating mucinous PLCs from non-mucinous PCLs. Further emphasis on the combined role of EUS morphology, FNA based cytology, and cyst fluid analysis for potential tumor and molecular markers may help to improve the overall accuracy of EUS FNA in the diagnosis of mucinous PCLs.

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Abbreviations

EUS	endoscopic ultrasound
FNA	fine needle aspiration
PCL	pancreatic cyst lesions
PCN	pancreatic cyst neoplasm
NMCLs	non-mucinous cystic lesions
MCL	mucinous cystic lesions
PC	pseudocyst
SCA	serous cyst adenoma
SPT	solid pseudopapillary tumor
PET	pancreatic endocrine tumor
IPMN	intraductal papillary mucinous neoplasms
CEA	carcinoembryonic antigen
LR	likelihood ratio
SROC	summary receiver operating characteristic
DOR	diagnostic odds ratio
AUC	area under curve

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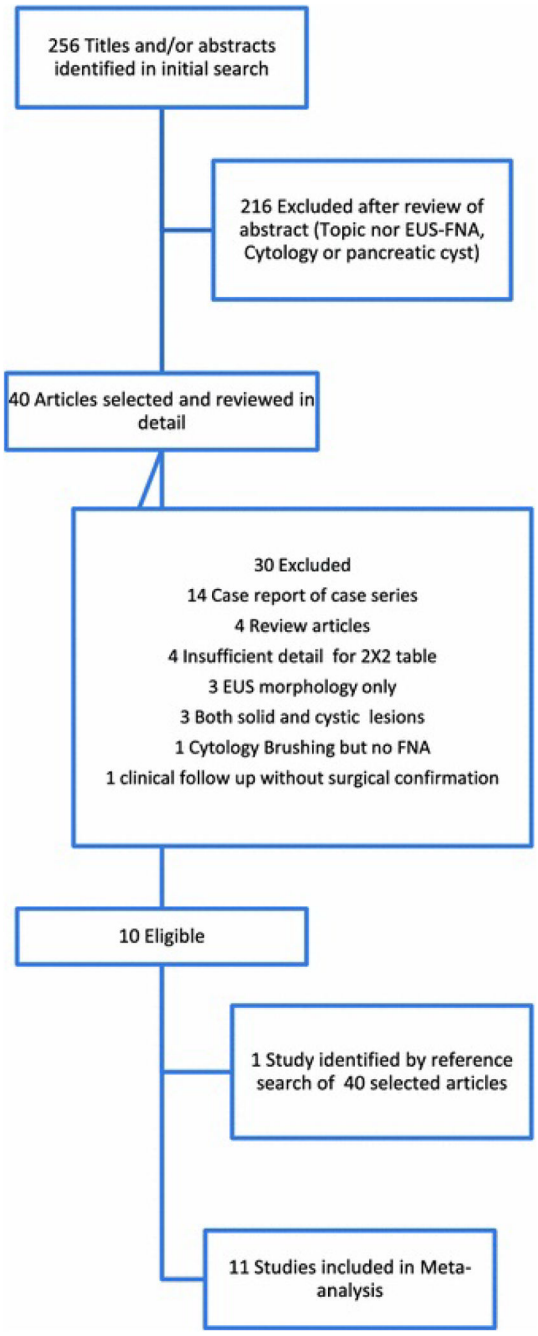

Figure 1.
Flow diagram of study selection process for the Systematic Review and Meta-analysis

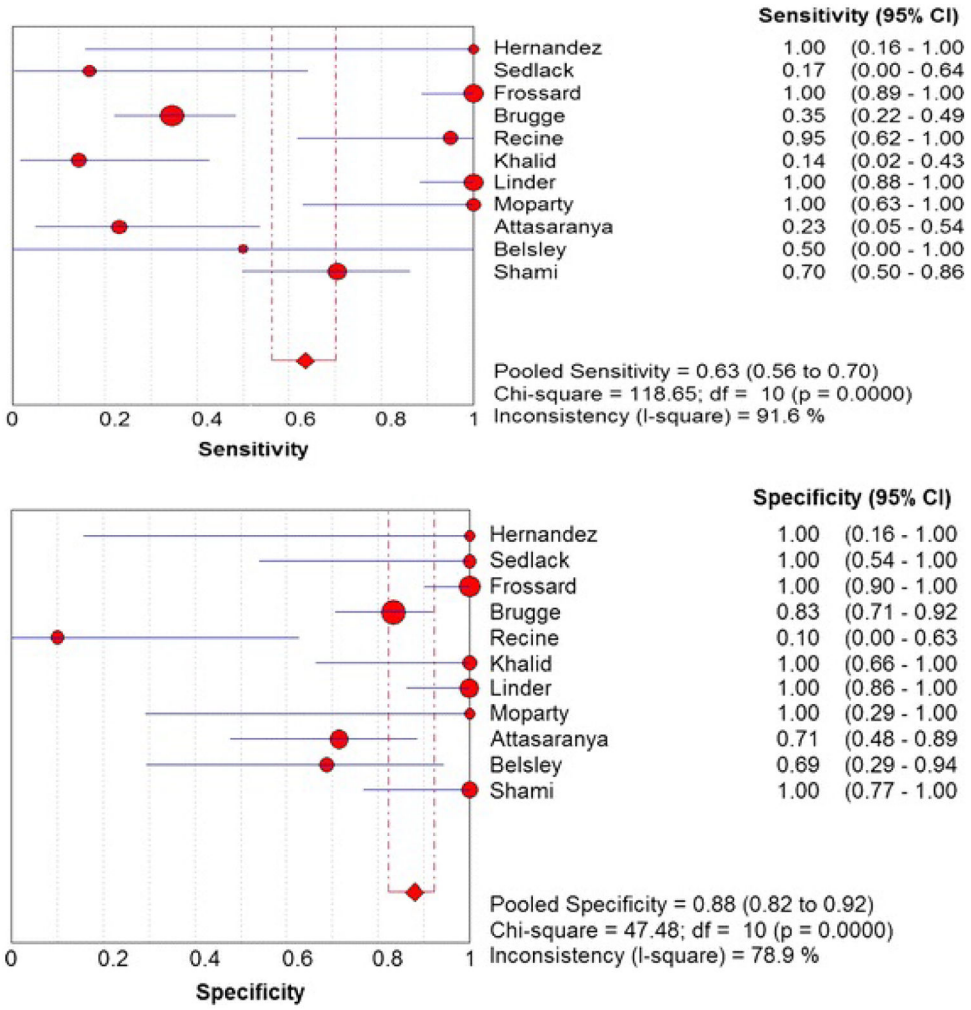

Figure 2.

Pooled sensitivity and specificity. The size of each *round* is proportional to the sample size for each study, and the *horizontal lines through the rounds* indicate a graphical representation of the 95% CI of that study. For the combined analysis, the *diamond and vertical dashed bar* indicates the pooled sensitivity or specificity, with the left and right ends of the *vertical bar* indicating the pooled 95% CI.

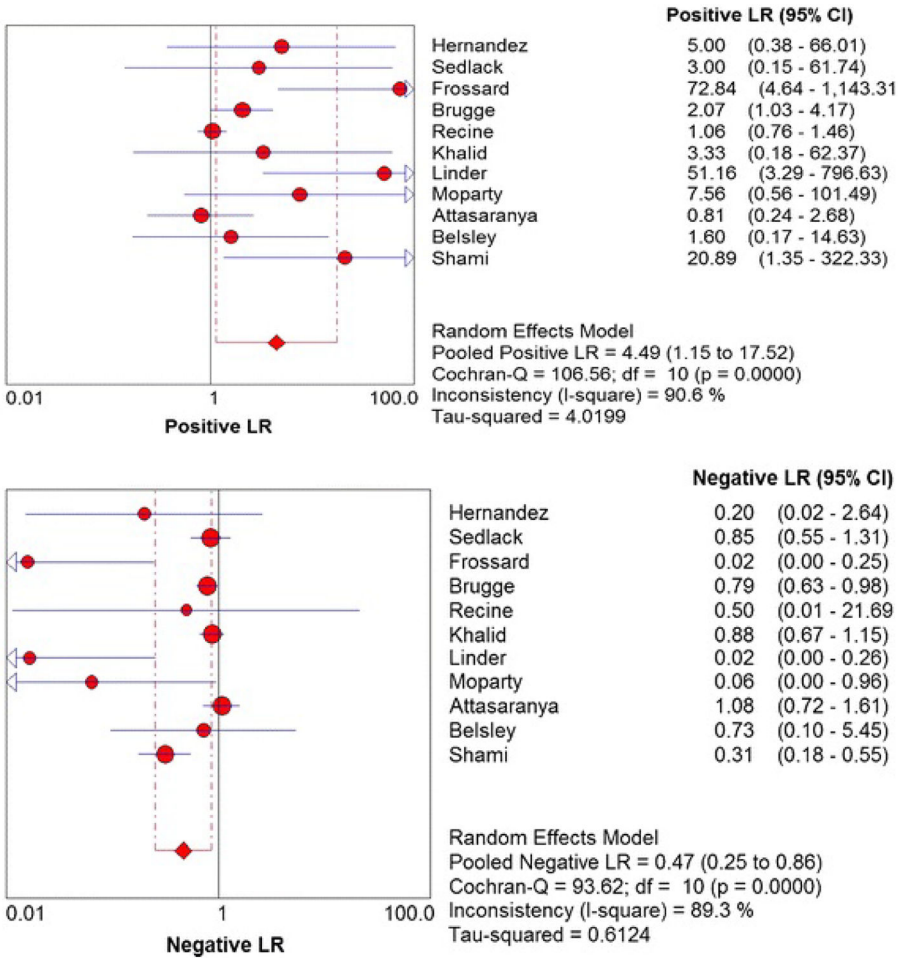

Figure 3.

Pooled positive and negative likelihood ratios. The size of each *round* is proportional to the sample size for each study, and the *horizontal lines through the rounds* indicate a graphical representation of the 95% CI of that study. For the combined analysis, the *diamond and vertical dashed bar* indicates the pooled positive or negative likelihood ratio, with the left and right ends of the *vertical bar* indicating the pooled 95% CI.

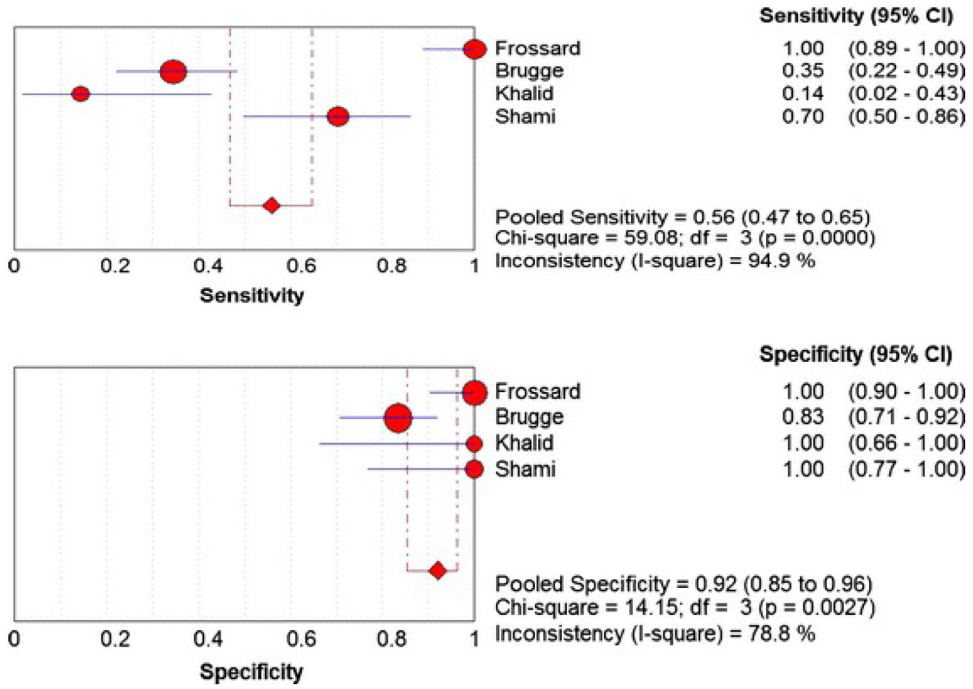

Figure 4.

Pooled sensitivity and specificity for all prospective studies. The size of each *round* is proportional to the sample size for each study, and the *horizontal lines through the rounds* indicate a graphical representation of the 95% CI of that study. For the combined analysis, the *diamond and vertical dashed bar* indicates the pooled sensitivity or specificity, with the left and right ends of the *vertical bar* indicating the pooled 95% CI.

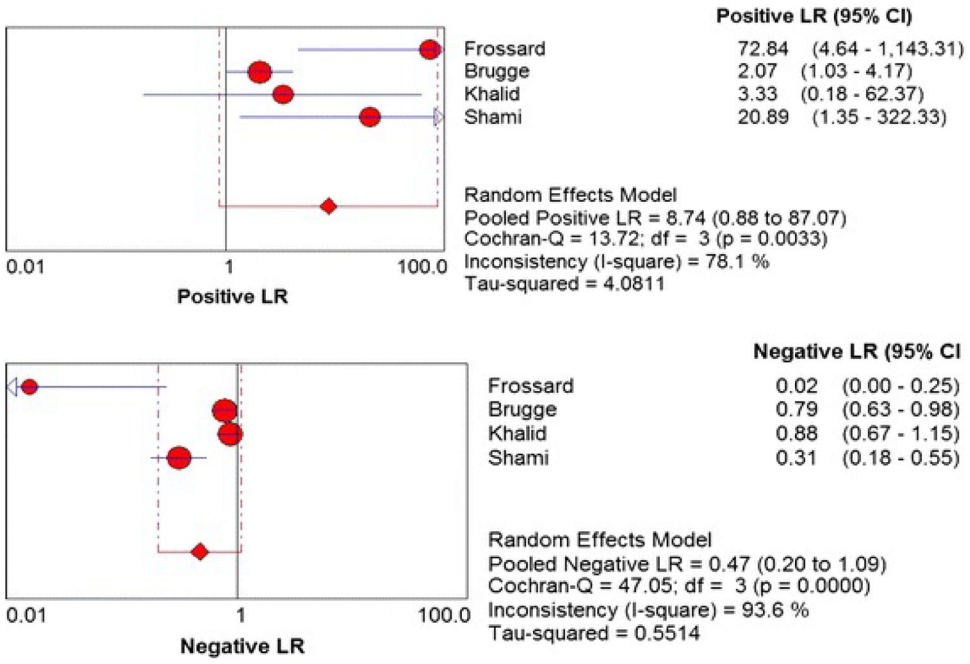

Figure 5.

Pooled positive and negative likelihood ratios for all prospective studies. The size of each *round* is proportional to the sample size for each study, and the *horizontal lines through the rounds* indicate a graphical representation of the 95% CI of that study. For the combined analysis, the *diamond and vertical dashed bar* indicates the pooled positive or negative likelihood ratio, with the left and right ends of the *vertical bar* indicating the pooled 95% CI.

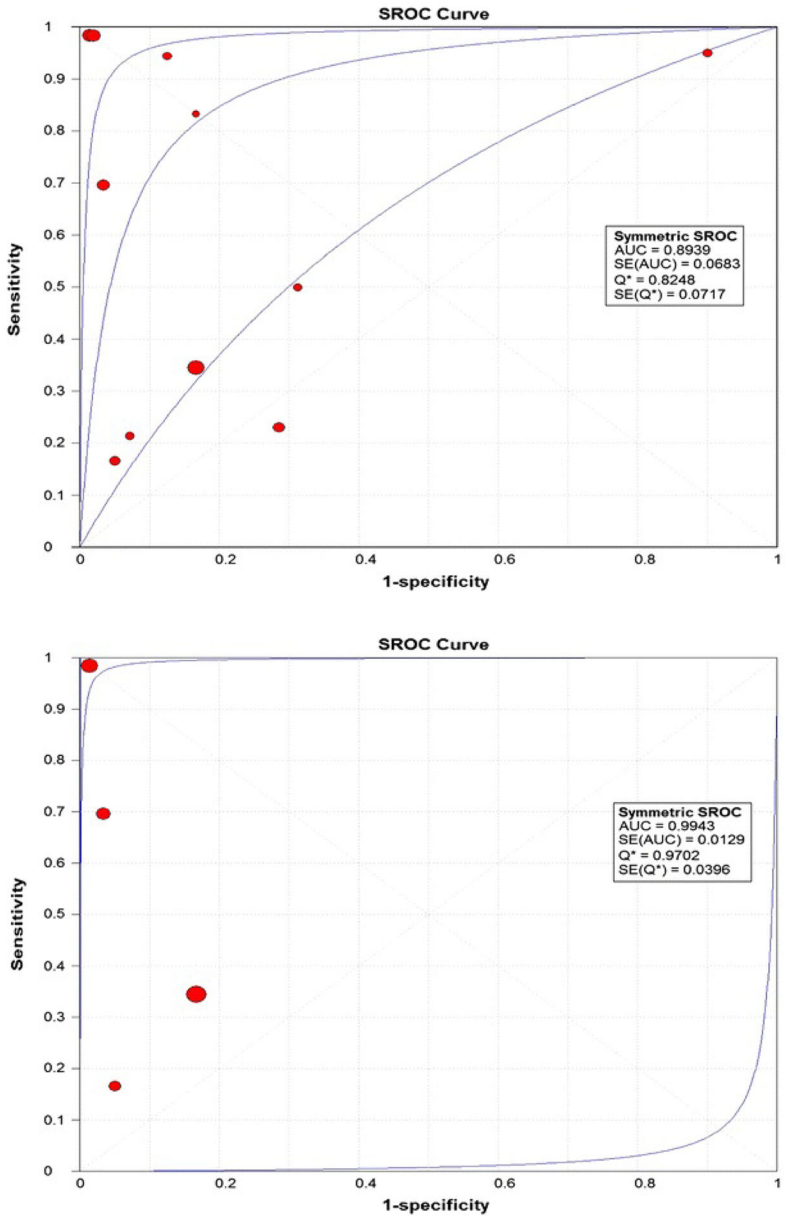

Figure 6.

Summary Receiver Operating Characteristic (SROC) Curve for all 11 studies of meta-analysis and SROC Curve for 4 prospective studies

Dig Dis Sci. Author manuscript; available in PMC 2014 September 19.

Table 1

Characteristics of included studies

Index	Study Detail	Study Design	Total	EUS-FNA	Surgery	Target Population *
1	Hernandez[22] 2002 USA	Retrospective	43	21	7	4
2	Sedlack[23] 2002 USA	Retrospective	111	18	34	12
3	Frossard[24] 2003 France	Prospective	127	127	67	67
4	Brugge[25] 2004 USA	Prospective	341	341	112	109
5	Recine[26] 2004 USA	Retrospective	13	13	13	13
6	Khalid[27] 2005 USA	Prospective	36	36	31	23
7	Linder[28] 2006 USA	Retrospective	102	102	71	55
8	Moparty[29] 2006 USA	Retrospective	45	30	11	11
9	Attasaranya[30] 2007 USA	Retrospective	48	48	48	34
10	Belsley[31] 2007 USA	Retrospective	28	9	9	7
11	Shami[32] 2007 USA	Prospective	43	43	43	41
			937	**788**	**446**	**376**

* Target population: Indicates group of people who satisfied all inclusion criteria: Satisfactory EUS-FNA diagnosis and final diagnosis by surgical biopsy or surgical resection and histology.

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Table 2

Mucinous Cyst Subtypes

Index	Author	MCA		Adenocarcinoma		IPMN		Total Mucinous	
		EUS FNA	Histology	EUS FNA	Histology	EUS FNA	Histology	EUS FNA	Histology
1	Hernandez	0	0	2	2	0	0	2	2
2	Sedlack	0	4	1	1	0	1	1	6
3	Frossard **	16	17	9	9	15	14	40	40
4	Moparty *	5	3	2	2	1	3	8	8
5	Attasaranya	0	10	3	3	0	0	3	13
6	Belsley *	2	0	0	0	0	0	2	0
7	Shami	7	12	6	6	6	9	19	27
		30	**46**	**23**	**23**	**22**	**27**	**75**	**96**
% of Correct Diagnosis		**56.52% (26/46)**		**100% (23/23)**		**77.78% (21/27)**		**72.91% (70/96)**	

* Both Moparty and Belsley had 2 false positive results for MCA by EUS-FNA

** Frossard had 1 false positive result for IMPN by EUS-FNA

Table 3

Meta-regression analysis to determine sources of heterogeneity for all 11 studies and subgroup of all prospective studies

Covariate	coefficient	p-value	RDOR	95% CI
Meta-analysis				
Sex (ratio of male vs. female)	−1.23	0.81	0.29	(0.0, >1000)
Sample size	0.09	0.31	1.09	(0.89, 1.33)
Design (prospective vs. retrospective)	0.24	0.94	1.27	(0.0, >1000)
Center (multi-center vs. single center)	−8.72	0.26	0	(0.0, >1000)
Country (America vs. non-America)	−1.73	0.75	0.18	(0.0, >1000)
Needle size*	−0.95	0.49	0.39	(0.02, 8.48)
Subgroup (Prospective Studies) Analysis				
Sex (ratio of male vs. female)	22.3	0.2	>1000	(0,>1000)
Sample size	−0.06	0.18	0.94	(0.75, 1.17)
Center (multi-center vs. single center)	−3.91	0.17	0.02	(0,>1000)
Country (America vs. non-America)	−5.61	0.48	0	(0,>1000)
Needle size	1.65	0.55	5.19	(0, >1000)

* based on uni-variate meta-regression and reduced data (centers = 10)