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Original article

Diagnostic yield of EUS-FNA-based cytology distinguishing malignant and benign IPMNs: A systematic review and meta-analysis



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ABSTRACT

Objectives: Differential diagnosis of malignant and benign intraductal papillary mucinous neoplasms (IPMNs) is essential to determine the optimal treatment. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is currently used to diagnose pancreatic cystic lesions worldwide, but few studies have focused on the diagnostic yield to distinguish malignant and benign IPMNs. Therefore, we aim to systematically review the diagnostic yield of EUS-FNA-based cytology to distinguish malignant and benign IPMNs.

Methods: Relevant studies with a reference standard of definitive surgical histology which published between 2002 and 2012 were identified via MEDLINE and SCOPUS. Malignant IPMNs included invasive adenocarcinoma, carcinoma in situ, and high-grade dysplasia.

Results: Four studies with 96 patients were included in this meta-analysis. For diagnostic yield of EUS-FNA-based cytology distinguishing malignant and benign IPMNs, the pooled sensitivity and specificity were 64.8% (95% CI, 0.44–0.82) and 90.6% (95% CI, 0.81–0.96), respectively. Similarly, the positive likelihood ratio and negative likelihood ratio were 6.35 (95% CI, 2.95–13.68) and 0.43 (95% CI, 0.14–1.34), respectively. Malignant IPMNs were observed in 20.8% (20/96) of patients in EUS-FNA studies.

Conclusions: EUS-FNA-based cytology has good specificity but poor sensitivity in differentiating benign from malignant IPMNs. Newer techniques or markers are needed to improve diagnostic yield.

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Introduction

Pancreatic cystic lesions are increasingly encountered in clinical settings, probably because of wider use of imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI) [1,2]. Such lesions comprise a wide range of disease entities, including cystic neoplasms (e.g., mucinous cyst neoplasm, intraductal papillary mucinous neoplasm [IPMN], and serous cyst

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neoplasm), benign cysts (simple cyst and pseudocyst), and cystic variants of solid neoplasms [3].

Among these lesions, IPMN has unique characteristics [3]. First, IPMN constitutes a broad pathological spectrum: hyperplasia (benign), low-grade dysplasia (adenoma), high-grade dysplasia (carcinoma in situ), and adenocarcinoma. Furthermore, most IPMNs can be classified into 2 types based on their primary location in the pancreatic duct: branch-duct or main-duct. Each type differs in risk of malignancy, which affects treatment recommendations. In a 2012 review of published studies [3], main-duct IPMN was determined to have a 61.6% mean frequency of malignancy (range, 36–100%), and the mean frequency of invasive lesions was 43.1% (range, 11–81%). Accordingly, the revised 2012 international consensus guidelines [3] recommended resection for all surgically fit patients with main-duct IPMN, especially in patients with high-risk stigmata (e.g., a main pancreatic duct diameter > 10 mm). In

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main-duct IPMN, a main-duct size between 5 and 9 mm is considered as a worrisome feature, and such lesions would be recommended for evaluation without immediate resection; however, a clear cytologic diagnosis of malignancy in such patients would change the decision to immediate resection. On the other hand, branch-type IPMN has less frequency of malignancy (range, 6.3–46.5%). Given the lower rates of malignancy, surveillance and follow-up are generally recommended for branch-duct IPMN without worrisome features (e.g., mural nodules, increasing in size). Here too, a cytologic diagnosis of malignancy can also significantly change the decision to proceed with an immediate surgical resection rather than continued surveillance.

A considerable number of studies utilizing imaging studies, cytology, and cystic fluid analysis (tumor markers, molecular markers, etc.) have attempted risk stratification in IPMN for appropriate management [4-6]. Among them, cytology is one of the most important factors for differentiating IPMNs and affects patients' management. Currently, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is widely accepted method to obtain cystic fluid from pancreatic cystic lesions for cytology and biochemistry analysis [3]. The majority of the literature on EUS-FNA-based cytology, especially in the United States and other Western countries, has focused on distinguishing mucinous from non-mucinous cystic lesions of the pancreas, rather than distinguishing a benign mucinous cystic lesion from a malignant mucinous cystic lesion. To the best of our knowledge, no detailed analysis has been done to summarize the diagnostic yield of cytology obtained from EUS-FNA for distinguishing malignant from benign IPMN. The aim of our study was to perform a systematic review of the available evidence on the diagnostic yield of cytology from EUS-FNA for distinguishing benign and malignant IPMNs.

Methods

Literature search

The review of previously published studies was performed by using published guidelines for conducting a systematic review [7]. First, we searched the literatures published from January 1, 1992 through October 5, 2012, using the MEDLINE and SCOPUS databases independently by two investigators (R.S. and S.A.). Articles listed ahead of publication were included. For EUS-FNA studies, the following keywords were used in the search: (a) pancreatic cyst, endoscopy, FNA; (b) EUS AND pancreas AND cyst; (c) EUS, FNA, pancreatic cystic neoplasm; and (d) pancreatic cystic tumors AND EUS. Moreover, we performed a manual search of references cited in the selected articles and of published reviews to identify any additional relevant studies.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: 1) the study design was a randomized control trial, prospective or retrospective study, nested case—control study, or population-based case—control study of EUS-FNA-based cytology; 2) the study incorporated a final pathologic diagnosis as IPMN by surgical biopsy or by histological examination of surgically resected specimen; and 3) the results were reported in sufficient detail to construct a diagnostic 2×2 table (true positive, false negative, true negative, and false negative).

Data extraction

The following data were extracted from each study: the first author's last name, publication year, country where the study was performed, study population database (total number of patients enrolled in the study, number of patients with IPMN who underwent a confirmatory diagnostic procedure and had sufficient data to construct a 2×2 table), the endoscopic procedure for cytology acquisition (aspiration, brushing), adverse events related to IPMN, prevalence of malignant IPMN, subtype of IPMN (branch-type or main-duct type), and numbers of true-positive, false-negative, true-negative, and false-negative findings for malignant IPMN. Data extraction was conducted independently by two investigators (R.S. and S.A.) with disagreement resolved by consensus and discussion with a third investigator (N.T.).

Quality assessment

The quality of the studies identified was assessed independently by two authors using the Standards for the Reporting of Diagnostic Accuracy (STARD) initiative criteria, which involved completing a 25-item checklist for each study. An article was deemed of adequate quality for inclusion in this analysis if it scored a minimum of 13 of 25 points on the STARD checklist. Articles with a score greater than 19 were deemed of high quality. Scoring was agreed on by consensus among the same authors as listed above.

Statistics

Based on comparison of the diagnosis from the result of EUS-FNA-based cytology of benign versus malignant IPMN against the final histopathological diagnosis, we re-constructed 2 x 2 statistical tables for each study. Where 0 counts occurred in at least one cell of a study's table, a continuity correction of 0.5 was added to every value for that study in order to calculate sensitivity and specificity. Based on the 2×2 tables, we calculated true-positive, false-positive, true-negative, and false-negative values. Meta-DiSc version 1.4 statistical software (Unit of Clinical Biostatistics team of the Ramón y Cajal Hospital, Madrid, Spain) was used to calculate the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic accuracy, and diagnostic odds ratio (DOR) (PLR/NLR) for malignant IPMN diagnosis for each study [8]. We used the DerSimonian-Laird random effects model to pool final sensitivity, specificity, PLR, NLR, and DOR [9]. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimates. Point estimates were plotted with 95%



Fig. 1. Flow diagram of the study selection process (EUS-FNA: endoscopic ultrasoundguided fine-needle aspiration, IPMN: intraductal papillary mucinous neoplasm).

Table 1

Characteristics	of	FUS-FNA	studies
Characteristics	UI.	LU3-IIM	studies.

EUS-FNA studies									
Article, Year, Country [Reference]	No. of patients	No. patients included in meta-analysis	No. patients with branch- type IPMN (%)	No. patients with malignant IPMN (%)	Length of study (months)	STARD score	Technical information	No. of adverse events (%)	
Wiesenauer, 2003, USA [19]	64	39	NA	12 (30.7)	166	16	Aspiration	NA	
Salla, 2007, Greece [20]	8	8	NA	3 (37.5)	26	15	Aspiration	NA	
Al-Haddad, 2010, USA [21]	37	6	NA	2 (33.3)	24	14	Brushing	NA ^a	
Genevay, 2011, USA [22]	112	43	43 (100)	3 (6.97)	180	16	Aspiration	NA	

EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; STARD, Standards for Reporting of Diagnostic Accuracy; NA, not available.

^a Number of adverse events related specifically to IPMN were indistinguishable from other cystic lesions in this study using brush cytology.

confidence intervals (CIs) for each cohort. A summary receiver operating characteristic (SROC) curve was constructed based upon the Moses-Shapiro-Littenberg method [10]. The area under the curve (AUC) of an SROC curve is a measure of the overall performance of a diagnostic test to accurately discriminate those with versus those without the condition of interest [10]. A well-performing test has an AUC close to 1, and a poor test has an AUC close to 0.5 [11]. The Q^{*} index was calculated as per the Moses-Shapiro-Littenberg method [10]. The Q^{*} index is defined by the point at which the sensitivity and specificity are equal, which is the point closest to the ideal top-left corner of the SROC space [10]. Heterogeneity was assessed by using χ^2 statistics, I² measure of

inconsistency and Cochran's Q test [12–14]. The χ^2 test, with degrees of freedom = number of studies – 1, was used to assess whether the observed differences in study results were compatible with chance alone. A *P*-value < .05 (or a large χ^2 statistic relative to degrees of freedom) was considered evidence of heterogeneity rather than of chance. The I² index describes the percentage of total variations across studies that are due to heterogeneity rather than chance. Generally, an I² index of 0%–40% excludes heterogeneity, an I² index of 50%–90% represent moderate heterogeneity [12]. The homogeneity of the likelihood ratio and DOR were tested by using Cochran's Q test based on inverse variance weights.



EUS-FNA Specificity



Fig. 2. Pooled analysis for (A) endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)-based cytology. Pooled sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) are shown. The size of each plot circle is proportional to the effect size for each study, and the horizontal line through each circle indicates the 95% confidence interval (CI) for that study. For the pooled analysis, the diamond indicates the pooled value, and the horizontal lines delineate the 95% CI for the analysis.

The robustness of the meta-analysis to publication bias was assessed by various bias indicators, including the Egger and failsafe N tests and the trim-and-fill method [15,16]. Funnel plots were constructed to evaluate the publication bias using the standard error and diagnostic odds ratio [17,18]. Analysis was done using the Comprehensive Meta-analysis Version 2 program (Biostat, Englewood, NJ). For all statistical methods used in the metaanalysis, a *P*-value < 0.05 was regarded as significant.

Results

Literature search

The detailed steps of our literature search are shown in Fig. 1. Briefly, we identified 224 potentially relevant titles and abstracts focusing on EUS-FNA and IPMN. Of those, 4 studies on EUS-FNA-based cytology were ultimately included in the meta-analysis [19–22].

Study characteristics

Among the 4 EUS-FNA-based cytology studies, 3 studies were from the United States and 1 was from Greece. There were 3 retrospective studies and 1 prospective study. In total, 96 patients had diagnostic EUS-FNA-based cytology and a final diagnosis of IPMN. The characteristics of the included studies are shown in Table 1.

Meta-analysis

Fig. 2 shows the forest plots of sensitivity, specificity, PLR, and NLR of the EUS-FNA-based cytology for distinguishing malignant and benign IPMNs. For EUS-FNA-based cytology, the pooled sensitivity and specificity were 64.8% (95% CI, 0.44–0.82) and 90.6% (95% CI, 0.81–0.96), respectively. Similarly, the PLR and NLR were 6.35 (95% CI, 2.95–13.68) and 0.43 (95% CI, 0.14–1.34), respectively. *P*-values for χ^2 heterogeneity, I² measure of inconsistency and Cochran's Q test and I for the pooled sensitivity are shown in Fig. 2.

There were insufficient data for us to extract data regarding EUS-FNA-based cytology techniques (3 studies with aspiration alone and 1 study with brush cytology). The overall accuracy of EUS-FNA-based cytology was explored by drawing SROC curves and finding the AUC (Fig. 3). For malignant IPMN detection, EUS-FNA-based cytology had an AUC of 0.94 for all 4 studies.

Table 1 summarizes the frequency of malignant IPMN. Malignant IPMNs were observed in 20.8% (20/96) of patients in the EUS-FNA studies. Limited data were available for the subtype of IPMN (branch- or main-duct type) and adverse events. There were insufficient variables for meta-regression analysis.

The funnel plots for publication bias are shown in Fig. 4. The Egger test did not suggest publication bias for EUS-FNA metaanalysis (P = 0.505). The fail-safe N test indicated that for the combined 2-tailed *P*-value to be no longer significant (*P*-value >0.05), it would take an additional 15 "null" studies for EUS metaanalysis. By using the random-effects model, the DORs and 95% CIs for the combined studies for EUS-FNA-based cytology were 18.24 (95% CI, 5.56–59.79), respectively.

Discussion

This systematic review summarizes 4 EUS-FNA-based cytology studies comprised a total of 96 patients who had EUS-FNA and were diagnosed with IPMN. To the best of our knowledge, this is the first meta-analysis to summarize the diagnostic yield of cytology obtained from EUS-FNA for distinguishing malignant from benign



Fig. 3. Summary of receiver operating characteristic (SROC) curve for endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)-based cytology for distinguishing malignant and benign intraductal papillary mucinous neoplasms. AUC: area under the curve; SE: standard error.

IPMN. Our results show that EUS-FNA-based cytology is 18 times likely to detect a malignant IPMN, with DORs of 18.24 (95% CI, 5.56–59.79). In pooled analysis of diagnostic yield distinguishing benign and malignant IPMNs, EUS-FNA-based cytology showed

Bias assessment for EUS-FNA based cytology



Fig. 4. Funnel plots for bias assessment of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)-based cytology.

high specificity and accuracy. However, sensitivity was unfortunately low, which denotes that we may misdiagnose a certain number of malignant IPMNs as benign IPMNs when we only rely on cytology.

We presume that the higher sensitivity and lower specificity that we observed in EUS-FNA-based cytology may be attributed to verification bias [23]. Verification bias occurs when out of all the patients who had a diagnostic test, only a subgroup of patients undergoes a confirmatory test. Verification bias can be avoided by requiring every patient who enrolls in the study to undergo the confirmatory test (e.g., surgical resection) irrespective of whether the diagnostic test (e.g., EUS-FNA) results are positive or negative. However, such a study design is not practical or ethical. It is reasonable to assume that the patients with a positive EUS-FNAbased cytology result would be more likely to undergo a confirmatory test compared to patients with a negative cytology result. For the same reason, specificity might be underestimated.

To conquer the problematic low sensitivity of cytology, cystic fluid analysis may be applied to distinguish between malignant and benign IPMNs or between non-mucinous and mucinous pancreatic cystic lesions. Cystic fluid analysis for tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and molecular markers such as mucin, has been applied to distinguish malignant and benign IPMN [4]. Maire et al. [5] performed EUS-FNA in 41 patients with IPMN. They reported that a cut-off value of 200 ng/ml for CEA in cystic fluid had a sensitivity of 90%, specificity of 71%, positive predictive value (PPV) of 50%, and negative predictive value (NPV) of 96% to distinguish malignant versus benign IPMN. Furthermore, a cut-off value of 40 U/ml for CA 72.4 showed sensitivity of 87.5%, specificity of 73%, PPV of 47%, and NPV of 96%. More recently, Farrell et al. reported promising role of micro-RNA 21 and micro-RNA 221 in pancreatic cystic lesions obtained from endoscopic technique as a biomarkers to distinguish benign and malignant pancreatic cystic lesions [24]. Regarding EUS-FNA technique for cytology acquisition, EUS-FNA aspiration plus brushing cytology may be a choice to improve diagnostic yield of EUS-FNA-based cytology to distinguish malignant and benign pancreatic cystic lesions as Thomas et al. reported [25]. These novel biomarkers and new endoscopic technique for cytology acquisition are quite promising, but more trials with larger sample sizes are required before they can be applied in clinical practice.

Our study limitations were small number and heterogeneity of included studies. Furthermore, subgroup analysis to determine the source of heterogeneity could not be made due to insufficient information. We would like to propose that well-designed prospective study should be conducted to clarify contributing factors which may affect diagnostic yield of EUS-FNA-based cytology to distinguish malignant and benign IPMNs (e.g., branch-duct or main-duct, with or without worrisome features).

In conclusion, EUS-FNA-based cytology has good specificity but poor sensitivity in differentiating benign from malignant IPMNs. Newer techniques and/or markers are needed to better distinguish malignant and benign IPMN.

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