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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.

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 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%

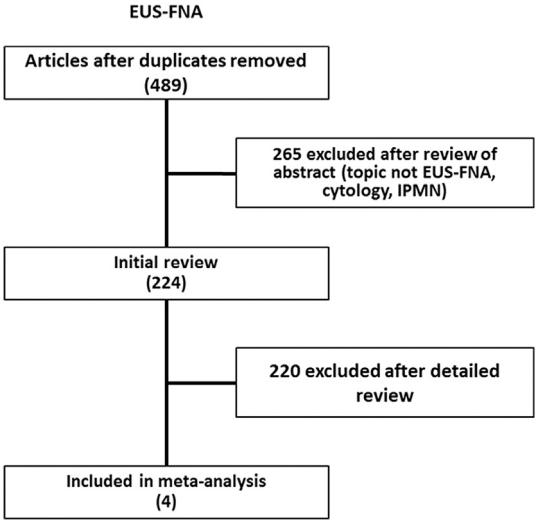

Fig. 1. Flow diagram of the study selection process (EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration, IPMN: intraductal papillary mucinous neoplasm).