EUS-FNA and ERCP in the Diagnosis of Presumed Malignant Biliary Obstruction: A Meta-analysis

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ABSTRACT
Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) and Endoscopic Retrograde Cholangiopancreatography (ERCP) are two choices for cytopathological diagnosis in patients with suspected malignant biliary obstruction. Our aim was to compare the sensitivity, specificity and likelihood ratio (LR) of EUS-FNA and ERCP in the diagnosis of presumed malignant biliary obstruction. In this meta-analysis, PubMed, SCOPUS and EMBASE databases were examined to find studies published from January 2000 to December 2015. No language restriction was applied. All the searched studies were retrieved, and their references were checked as well for other relevant publications. The main outcome measurements were sensitivity, specificity and likelihood ratio. Three studies were selected for the analysis on the basis of inclusion criteria. The overall pooled sensitivity and negative likelihood ratio (LR-) of EUS-FNA for diagnosis of malignant biliary obstruction were 81.4% [95% CI 74.1–87.4%] and 0.187 (95% CI 0.050–0.699), respectively and the overall pooled sensitivity and LR- of ERCP for diagnosis of malignant biliary obstruction were 35.0% [95% CI 26.5–44.4%] and 0.770 (95% CI 0.666–0.890), respectively. The meta-analysis suggests that EUS-FNA was superior to ERCP in diagnosing malignant biliary obstruction.

Index Terms - EUS-FNA; ERCP; malignant biliary obstruction

1.0 INTRODUCTION

Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) is an accurate modality for the diagnosis of nodal metastases, pancreatic tumors, and perirectal malignancy, as well as has a well-established sensitivity for suspected malignant biliary obstruction, ranging from 85% to 93% in recent studies [1, 2, 3, 4, 5].

Prior to the development of EUS, Endoscopic Retrograde Cholangiopancreatography (ERCP) with biliary brush cytology or biopsy was the initial investigation of choice for cytopathological diagnosis in patients with suspected malignant biliary obstruction, such as pancreaticobiliary malignancy. Although this technique has a specificity approaching 100%, sensitivity for malignancy has been reported as 15-65% in strictures secondary to pancreatic cancer and 44-80% in strictures due to cholangiocarcinomas, and the overall sensitivity is 42% [6, 7].

EUS allows excellent visualization of the pancreas and adjacent organs and has evolved as a sensitive staging modality for pancreatobiliary malignancy [8, 9, and 10]. The addition of EUS-FNA allows cytological diagnosis of pancreatic masses. This has been shown, in many published series, to be highly accurate in diagnosing pancreatic masses [2, 11, 12]. In a retrospective multicenter study EUS-FNA was diagnostic of malignancy in 71% of solid pancreatic masses [13]. This conveys a significant advantage over traditional ERCP-based cytology. EUS-FNA is also preferred over percutaneous tissue biopsy because of a better yield and lower risk of tumor seeding.

Despite the widespread pervasiveness of ERCP and increasing availability of EUS at many centers, there are scant data that directly compare the 2 modalities in terms of tissue sampling. In view of reports were very rare and a single study was more likely lack of credible peace, therefore, we performed a meta-analysisof the published literatures to compare the sensitivity and specificity of EUS-FNA and ERCP in the diagnosis of presumed malignant biliary obstruction, as well as to quantify the potential between-study heterogeneity.

2.0 METHOD

2.1 Publication search

A bibliographic search was performed in PubMed, SCOPUS and EMBASE by using the following terms: (“Endoscopic ultrasonography-guided fine needle aspiration” or “EUS-FNA”) and (“Endoscopic Retrograde Cholangiopancreatography” or “ERCP”) and “Malignant Biliary Obstruction”. No language restriction was applied. All the searched studies were retrieved, and their references were checked as well for other relevant publications. Review articles were also looked up to find additional eligible studies. The inclusion criteria were (1) evaluation of EUS-FNA comparison with ERCP in the diagnosis of presumed malignant biliary obstruction and the data needed to be sufficient to calculate the sensitivity and specificity, (2) randomized controlled trials (RCT) or controlled clinical trials (CCT), (3) confirmation of Malignant Biliary Obstruction by histopathology at the time of surgery or inoperable at the time of surgery or autopsy was used as the reference standard. Any differences were resolved based on the statistical criteria as described below. The data needed to be sufficient to calculate the sensitivity and specificity. Studies that accepted a ‘positive for malignancy’ or ‘suspicion of malignancy’ cytological interpretation as indicative of malignancy were included. The exclusion criteria were (1) studies with insufficient data; (2) reviews, editorials, correspondence letters that did not report their own data and (3) case reports and studies with fewer than 10 patients.

2.2 Statistical Methods

The index test was use of EUS-FNA and ERCP with studies reporting ‘positive for malignancy’ or ‘suspicion for malignancy’ in our analysis. Assessment of methodological quality were based on Jadad scoring system [14]. The included studies were analyzed according to the methodology suggested by the Cochrane DTA Working Group [15]. This methodology gives more clinically useful results, as it is focused on two statistical measures of diagnostic accuracy: the sensitivity of the test (the proportion of those with the disease who have an abnormal test result) and the specificity of the test (the proportion of those without the disease who have a normal test result). Only studies in which we were able to obtain data to populate 2x2 tables were included. Initial analysis was performed using the Review Manager (Rev Man 5.3, Copenhagen: The Nordic Cochrane

Centre, The Cochrane Collaboration). After preparing and exporting data from Rev Man, we used the Meta-disc version 1.40 for meta-analysis of diagnostic accuracy studies. It involves computing the pooled sensitivity and specificity, and to plot the summary receiver operating characteristics curve with summary point and corresponding 95% confidence region.

3.0 RESULTS

3.1 Article Search and Methodological Quality of Included Studies

The initial literature search identified 9 studies. Based on the inclusion criteria, 6 studies were excluded, with a selection of 5 studies for more detailed review (Fig 1). The following information was extracted from each study: the first author, published year, country of study population, and dates of both EUS-FNA and ERCP (Table 1). The methodological quality of the included studies, as assessed by the Jadad scoring system, is shown in Table 2. In general, the quality of the studies was moderate to good (all ≥ 3). All data were analyzed in accordance with the intention-to-treat principle.

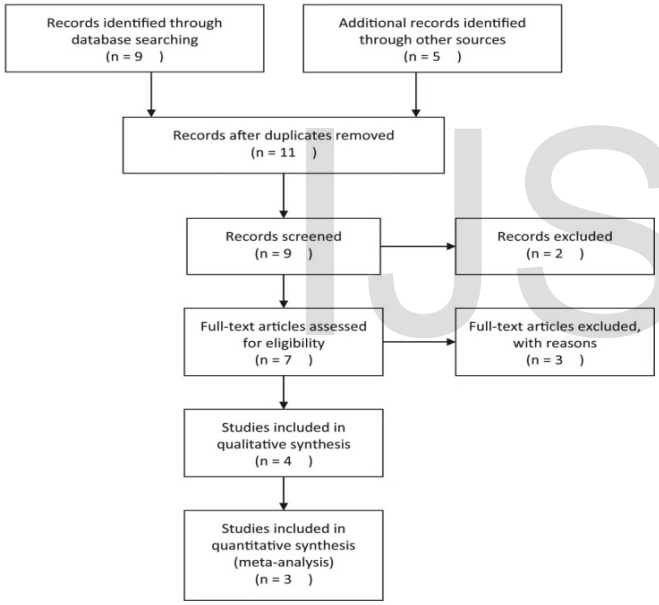

Fig 1: Chart for selection of trials

TABLE 1
Characteristics of studies included in this meta-analysis

Author	Year	Original Country	EUS-FNA	ERCP	Final diagnoses	Reference standards	Result included in the analysis
Oppong K et al. [19]	2010	United Kingdom	18 Positive 07 Suspicious 14 Negative	10 Positive 12 Suspicious 17 Negative	34 Malignant 05 Benign	Surgery, diagnostic histology or cytology, clinical follow-up	Only positive
Wasan SM et al.[18]	2005	United States	56 Positive 03 Suspicious 31 Negative	07 Positive 05 Suspicious 60 Negative	66 Malignant	Surgery	Only positive
Weilert F et al.[20]	2014	United States	41 Positive 07 Suspicious 03 Negative	15 Positive 17 Suspicious 12 Negative 07 Non-diagnostic	48 Malignant 03 Benign	Surgery, sampling at the index procedure, a second EUS-FNA, long-term follow-up	Both positive and suspicious

TABLE 2
Jadad score

Author	Year	Country	Randomization	Blinding	Withdrawal	Total
Oppong K et al.	2010	United Kingdom	1	1	1	3
Wasan SM et al.	2005	United States	1	1	1	3
Weilert F et al.	2014	United States	1	1	1	3

3.2 Sensitivity and negative likelihood ratio for EUS-FNA

The overall pooled sensitivity and negative likelihood ratio (LR-) of EUS-FNA for diagnosis of malignant biliary obstruction were 81.4% [95% CI 74.1–87.4%] and 0.187 (95% CI 0.050–0.699), respectively (Fig 2).

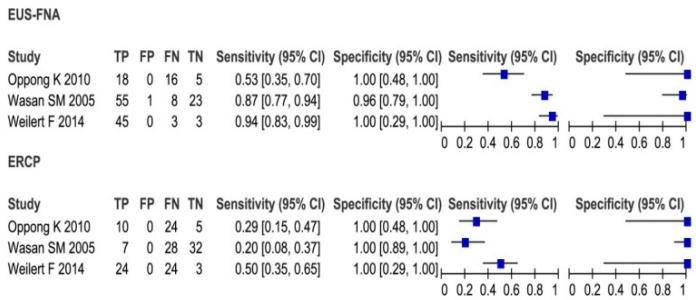

Fig 2: Meta-analysis of EUS-FNA vs. ERCP in diagnosing malignant biliary obstruction

3.3 Sensitivity and negative likelihood ratio for ERCP

The overall pooled sensitivity and LR- of ERCP for diagnosis of malignant biliary obstruction were 35.0% [95% CI 26.5–44.4%] and 0.770 (95% CI 0.666–0.890), respectively (Fig 2).

3.4 Summary receiver operating curve (SROC) for EUS-FNA and ERCP to diagnose malignant biliary obstruction

The SROC result showed that EUS-FNA was superior to ERCP in diagnosing malignant biliary obstruction (Fig 3).

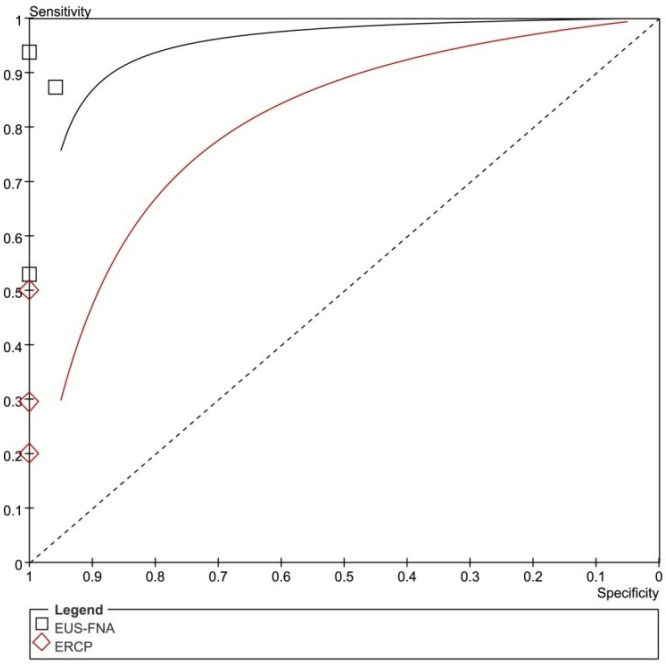

Fig 3: Summary receiver operating curve (SROC) for EUS-FNA vs. ERCP in diagnosing malignant biliary obstruction

4.0 CONCLUSION

The pre-test probability of malignancy is high and has been reported as greater than 90% in a patient presenting with a pancreatic mass and jaundice. The differential diagnosis of pancreatic adenocarcinoma includes focal chronic pancreatitis, autoimmune pancreatitis and pancreatic neuroendocrine tumor [16, 17]. An accurate preoperative diagnosis is desirable but is not absolutely necessary because most patients will undergo attempted resection based on the presence of a mass and obstructive jaundice. Insisting on a confirmed diagnosis of malignancy in fit patients with an operable suspicious lesion in the head of the pancreas can delay surgery and allow the tumor to progress. In elderly and comorbid patients, however, confirmation of the diagnosis preoperatively should be sought more keenly since surgery carries a greater risk and is best avoided in those without malignancy. CT is the first investigation of choice in patients with suspected pancreatic cancer. The absence of a mass on CT, however, is an indication for EUS which has an important role in clarifying the diagnosis prior to surgery [8]. In those patients with unresectable disease, chemotherapy is the treatment of choice. In patients with benign disease, such as obstructive jaundice due to bile duct stone, surgery is often the most appropriate treatment, since symptoms caused by biliary obstruction and duodenal stenosis can be effectively treated. Chemotherapy is contra-indicated in those who may have benign disease and therefore positive histology or cytology is essential in those patients who are to be treated by non-surgical treatments.

Refer to the complications, major complications occurred in 12: pancreatitis (6), cholangitis (2), hemobilia (1), bacteremia (1), fever (1) and abdominal pain (1) in the study of Wasan SM et al [18]. And there were two complications occurred in Oppong K et al's study [19]. One patient had a mild attack of pancreatitis and one patient failed to drain and required a stent change a week later. Weilert F et al did not talk about the complications in their paper [20].

We performed this analysis and received a consistent result with those studies that EUS-FNA had excellent sensitivity and accuracy for the investigation of malignant biliary obstruction. Overall, EUS-FNA is superior to ERCP tissue sampling, and this is especially true for pancreatic masses.

Oppong et al performed a retrospective analysis of EUS-FNA compared with ERCP brushings in a series of 37 patients with suspected malignant obstruction. In their study, ERCP was performed before EUS-FNA, procedures were performed in a single session in only 56% of cases, on-site cytopathology was not available, and only 1 patient had cholangiocarcinoma in their cohort. They found that EUS-FNA had a higher sensitivity compared with ERCP brushings for diagnosing malignancy (53% vs 29%), when using strict cytologic criteria for malignancy.

Strengths of Weilert F et al's study include that all procedures were performed in a single session (reducing any potential time confounders), blinding of the second endoscopist performing ERCP tissue sampling, and the presence of on-site cytopathologic assessment, which has been shown to improve yield. They pointed out that EUS-FNA should be performed before ERCP in patients with suspected malignant biliary obstruction, and this issue was challenged by a previous study from Curcio G et al's group [21]. They evaluated intraductal aspiration (IDA) as a new sampling technique (brushing plus scraping and aspiration) in suspected malignant biliary strictures. To perform IDA, they removed the brush from its catheter. The tip of the catheter was then scraped back and forth across the stricture at least 10 times. The catheter and a suction device were then connected to a specimen trap to obtain intraductal aspiration of fluids and samplings. IDA showed a significantly higher sensitivity than brushing (89% vs. 37%; P<0.001) and had superior cellular adequacy (92.8% vs. 35.7%; P<0.001), appearing safe, simple, rapid, and applicable during routine diagnostic ERCP, with no additional costs. They pointed out that IDA could easily and significantly improve the diagnostic accuracy of ERCP, which is even more important in peripheral centers not equipped for routine EUS-FNA.

Weilert F et al indicated a huge overall difference of sensitivity and accuracy (90% to 94%) for EUS-FNA compared with a dual-sampling ERCP technique (50% to 53%), and mainly concentrated on comparing 2 sampling techniques, it is simply natural for them to find the superiority of EUS-guided FNA over ERCP-guided biliary sampling techniques in patients with pancreatic masses. This is because pancreatic tumors mostly lead to compressive biliary obstruction rather than invasion into the biliary tree. Practically, nobody ever tries useless ERCP-guided biliary sampling techniques in patients with a pancreatic mass lesion. Furthermore, the comparative data of EUS-FNA and ERCP-guided samplings in patients with mass-forming and or non–mass-forming intrinsic biliary strictures seems to be more important. EUS-FNA was reported to be equal in sensitivity and specificity to ERCP-guided sampling techniques in 19 patients with biliary strictures. Nevertheless, a flaw with these data is that the authors used an on-site cytopathologist to evaluate the sufficiency of EUS-FNA samplings and they did not do the same thing for ERCP-guided brushing or biopsy samplings. On-site cytopathology, which is known to improve EUS-FNA accuracy by 20%, could do the same for the accuracy of the ERCP samplings. Another feature of this article is that although ERCP-based sampling failed in 7 cases and those cases were non-diagnostic, the authors did not exclude them from.

To conclude, this meta-analysis summarizes available evidence regarding the diagnostic performance of EUS-FNA and ERCP in the detection of presumed malignant biliary obstruction. Our study suggests that EUS-FNA was superior to ERCP in diagnosing malignant biliary obstruction.

ETHICAL ISSUES

The authors declare no competing financial interest.

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