TRABAJOS ORIGINALES

Endoscopic ultrasound cytologic brushing *vs* endoscopic ultrasound – fine needle aspiration for cytological diagnosis of cystic pancreatic lesions. A multicenter, randomized open-label trial

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Received: 10/01/2018 · **Accepted:** 18/02/2018

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ABSTRACT

Introduction: the incidence of cystic pancreatic lesions (CPL) in the asymptomatic population is increasing. Achieving a preoperative diagnosis of CPL still remains a challenge.

Objectives: to evaluate the diagnostic accuracy of the cytological diagnosis of CPL from samples obtained by cytology brush *versus* standard endoscopic ultrasound fine needle aspiration (EUS-FNA).

Methods: a multicenter, randomized, open-label trial was performed of EUS-cytology brush (EUS-EB) *versus* EUS-FNA for the cytological diagnosis of CPL. Patients that underwent EUS-FNA with a CPL > 15 mm were included and randomized into two groups: group I, EUS-EB; group II, EUS-FNA. The final diagnosis was based on the histological evaluation of surgical specimens and clinical parameters, imaging and a five year follow-up in non-operated patients. The main outcome was the diagnostic accuracy of both methods. Secondary outcomes were the diagnostic adequacy of specimens and the rate of adverse events. Data were compared using the Chi-squared test. An intention to treat (ITT) and per-protocol (PP) analysis were performed.

Results: sixty-five patients were included in the study, 31 in group I and 34 in group II. Three patients initially randomized to group I were changed to group II as it was impossible to obtain a sample using the brush. The mean size of the CPL was 28.2 mm (range 16-60 mm). The diagnostic accuracy of EUS-EB was not superior to EUS-FNA, neither in the ITT nor the PP analysis (44.8% *vs* 41.1%, p = 0.77 and 38.4% *vs* 45.9%, p = 0.55).

Conclusions: EUS-EB does not improve the diagnostic accuracy of CPL in comparison with EUS-FNA.

Key words: Cytodiagnosis. Endoscopic ultrasonography. Endoscopic ultrasound-guided fine needle aspiration. Neoplasms. Cystic. Mucinous and serous. Pancreatic cyst.

INTRODUCTION

The incidence of cystic pancreatic lesions (CPL) is estimated at around 2.6% in the asymptomatic population and increases with advancing age (1). Despite improvements in imaging tests during recent years, achieving a definitive preoperative diagnosis in routine clinical practice remains a challenge.

The target of our efforts in clinical practice must be used to recognize cystic tumors among the different CPL. Within this pathology, cystic mucinous neoplasms such as mucinous cystadenoma or intraductal papillary mucinous neoplasms (IPMN), which have malignant potential, must be distinguished from non-mucinous or benign lesions such as serous cystadenoma or pseudocysts. The latter can be managed conservatively unless symptoms develop (2). In this setting, endoscopic ultrasound (EUS) is an essential tool, not only to identify small cysts but also to provide important details for their characterization. However, it is not possible to differentiate between neoplastic and non-neoplastic lesions only by the morphological features provided by EUS. Therefore, EUS-FNA is often performed in order

Lariño-Noia J, de-la-Iglesia D, Iglesias-García J, Macías M, López-Martín A, Legaz ML, Vila J, Reyes A, Abdulkader I, Domínguez-Muñoz JE. Endoscopic ultrasound cytologic brushing *vs* endoscopic ultrasound – fine needle aspiration for cytological diagnosis of cystic pancreatic lesions. A multicenter, randomized open-label trial. Rev Esp Enferm Dig 2018;110(8):478-484.

DOI: 10.17235/reed.2018.5449/2017

to obtain cells for cytological evaluation or the analysis of intracystic markers (2,3). The samples obtained by EUS-FNA in CPL generally have a poor cellularity, which decreases the accuracy of cytological evaluation in this scenario. Previous meta-analyses have shown a diagnostic sensitivity of 54% in this setting (4).

EchoBrush® (ECHO-19-CB; Cook Medical, Bloomington, Ind.), a cytology brush designed for use via a 19G EUS needle has been introduced into the market in order to improve the diagnosis yield. It allows a direct sampling of cystic pancreatic epithelium under EUS guidance. Previous trials have reported an increase of diagnostic sensitivity using this brush for the differential diagnosis of CPL (5-7). The objective of the present multicenter and randomized trial was to compare the diagnostic accuracy of samples obtained by EUS-EB *versus* EUS-FNA for the differential diagnosis of CPL.

METHODS

Study design

A multicenter, randomized, open-label trial.

Participants

Inclusion criteria

Patients referred for EUS guided sampling of a CPL with a diameter greater than 15 mm in one of the axes, from six different hospitals, over a one year period were evaluated for inclusion into the study.

Exclusion criteria

Patients were excluded from the study that did not understand or sign the informed consent and cases where EUS-FNA was impossible due to the following reasons: international normalized ratio (INR) of 1.5 or greater, platelet count less than 50,000/ml, unstable cardiovascular status and anticoagulant/antiplatelet drug intake.

Interventions

Demographics, pre-EUS investigations (medical records, toxic habits and previous pancreatic diseases) and procedures (CT abdominal scan and magnetic resonance cholangiopancreatography [MRCP]), details of EUS-FNA (size, location, fluid appearance, intracystic markers and cytological evaluation) and post-procedure adverse events were evaluated.

EUS procedure and cyst wall brushing

Patients received various combinations of intravenous midazolam, meperidine and fentanyl under appropriate cardiorespiratory monitoring prior to the EUS procedure. EUS was performed using the Pentax linear equipment attached to a Hitachi ultrasound platform. EUS-FNA was performed using 19G, 22G and 25G needles (EchoTip® Ultra needle) and the cytology brush, EchoBrush® (EB) (Cook Medical, Bloomington, Ind.). This device is intended for single use only and it is advanced through a 19-gauge needle. When multiloculated lesions were detected, the largest locule was sampled and brushed. Seven endosonographers with a minimum experience of 200 EUS procedures per year who had previously used the EchoBrush® device participated in the study. All patients were given prophylactic antibiotics during or shortly after the procedure (ciprofloxacin 400 mg intravenously as a single dose), and these were provided orally (500 mg bid) for three days after the procedure.

With regard to patients randomized to group I (EUS-EB group), the cyst was punctured using a 19G needle, the stylet was removed and the brush was introduced through the needle and advanced into the cyst under EUS guidance. The brush was then moved to and fro repeatedly against the inner wall of the cyst, ensuring an adequate contact with the cystic wall (Fig. 1). The brush was targeted towards nodules or solid components when they were identified on the EUS image. Subsequently, the brush was removed from the needle and spread onto slides and air-dried, methanol-fixed for Diff-Quik stains and ethanol-fixed for Papanicolau stains. Afterwards, the tip of the brush was cut-off and placed into a special cytologic preservation solution with the rest of the aspirated fluid at the end of the procedure for further cytological evaluation or cell-blocks. On site cytopathology interpretation was not routinely requested. When possible, fluid material was sent for biochemical evaluation of intracystic markers (amylase, carcinoembryonic antigen [CEA], Ca 72.4 and CA 15.3).

With regard to patients randomized to group II (EUS-FNA group), the puncture was performed using 19G, 22G or 25G after identifying the lesion. Smear samples were spread onto slide and air-dried, methanol-fixed for Diff-Quik stains and ethanol-fixed for Papanicolau stains. The rest of the fluid was added to a special cytolit solution for further cytological evaluation or cell-block preparation. As previously mentioned, a biochemical evaluation of intracystic markers was performed.

Cytohistological evaluation

Cytopathologists from the six participating centers filled in a specific report which included the following informa-

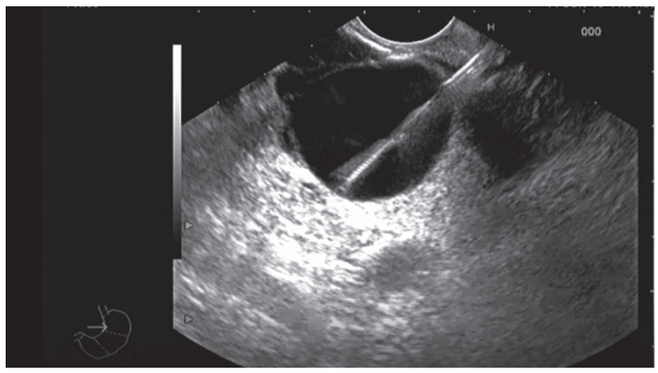

Fig. 1. *EUS-FNA with EchoBrush® (EB). See the hyperrefringent distal tip of the brush.*

tion: a) cellularity of the specimen that was graded using three levels (1: poor; 2: moderate; 3: rich); b) presence or absence of atypia/suspicious of malignancy or adenocarcinoma; c) cellular type: inflammatory cells, cuboidal cells staining positive for glycogen, mucinous epithelial cells; and d) cytological diagnosis when possible, including an indeterminate/inconclusive diagnosis and inadequate sample for evaluation.

Follow-up assessment

Patients without a definitive diagnosis based on the histology surgical specimens were followed up annually or biannually for up to five years with clinical, radiological and endoscopic evaluation. Patients were monitored for the development of malignancy or any symptoms related to the cyst. When necessary, patients were referred for surgery according to the criteria of each hospital. A presumptive diagnosis in non-operated cases was provided at the end of follow-up and was the final diagnosis used for the analysis.

Assessment of adverse events

All adverse events were assessed immediately post-procedure (up to two hours) and after a week by phone or in person. These included: a) intracystic bleeding: a hyperechogenic spot inside the cyst after puncture and/or a decrease in the hemoglobin level of 2 gr with or without a blood transfusion; b) post-procedure acute pancreatitis: abdominal pain with increased levels of pancreatic enzymes after EUS-FNA; and c) cyst infection: a fever exceeding 38 °C post-EUS-FNA in the absence of other etiology.

Outcomes

Primary outcome

The primary outcome was the diagnostic accuracy of both methods, considered as the percentage of a correct diagnosis according to the final diagnosis. The final diagnosis was based on histological specimens when cysts were resected or with a combination of clinical parameters, imaging tests, morphological features by EUS, intracystic markers (CEA and amylase) and cytological diagnosis when conclusive, after a minimum period of five years of follow-up.

Secondary outcome

Diagnostic adequacy was defined by the cytopathologists using a specific report according to the cellularity of samples. A sample was considered as adequate when a moderate and rich cellularity was obtained and inadequate when a poor cellularity was reported. The rate of adverse events was also assessed.

Sample size

Sample size was calculated on the basis of the probability sampling method. Data from the Al-Haddad study (15) were used and an increased sensitivity of 38% for the EUS-EB *versus* EUS-FNA was hypothesized with a confidence level of 95%, statistical power of 80%, and sample size of 62 patients. A total number of 65 patients should be included to correct for a potential loss of 5% of patients.

Randomization

The study subjects were randomized either to group I (EUS-EB) or group II (EUS-FNA). Randomization was performed in blocks of two and the randomization sequence was listed in a protocol that was open to the investigator and kept in the endoscopy room of each center.

Statistical analysis

Data are shown as the mean and standard deviation, percentages, median and range and odds ratio with the 95% confidence interval as appropriate. A comparison between groups was performed using the Student's t-test for numerical data, Pearson's Chi-squared test or Fisher's exact test for nominal data, and Wilcoxon rank test when appropriate. A p value of 0.05 or less was considered as statistically significant. Two types of analysis were performed, PP and ITT analysis.

Ethical clearance

The study was approved by the local Institutional Review Committee of each of the six different Spanish hospitals that participated in the study (REF 2008/56). The purpose of the study was explained clearly to the patients and their written informed consent was obtained. The CONSORT guidelines were followed for the conduct of a randomized study.

RESULTS

A total of 65 CPL were punctured in 65 patients over a period of one year. The characteristics of the cystic lesions evaluated in both groups are shown in table 1. Thirty-one lesions were randomized to group I and 34 to group II (ITT analysis group). Due to the inability of the use of the brush in three lesions located in the head of the pancreas, 28 patients were finally included in group I and 37 patients in group II. The brush could not be advanced out of the needle in two cases, and in one case the lesion could not be punctured with a 19G needle. It was not possible to obtain the final diagnosis in two cases and therefore, they were excluded from the diagnostic accuracy analysis (both were initially allocated in group I) (Fig. 2).

The final diagnosis of CPL is detailed in supplementary table 1: 30 IPMNs (47.6%), eleven pseudocysts (17.4%), ten serous cystadenomas (15.9%), four mucinous cystadenomas (6.4%), seven pancreatic adenocarcinomas with cystic degeneration (11.1%) and one PanIN lesion (1.6%) were identified. The final diagnosis was achieved by surgery in 13 patients (20.6%) and by follow-up in the remaining 50 patients (79.4%). The cytological diagnosis is shown in supplementary table 2. The proportion of patients with an indeterminate diagnosis or inadequate material for diagnosis in

Table 1. *Characteristics of patients and cysts in the EUS-EB group and EUS-FNA group (per protocol analysis)*

	EUS-EB (n = 28)	EUS-FNA (n = 37)	p
Age, median (range), years	69.5 (54-78)	71.5 (51.5-76.5)	0.695*
Male sex, n (%)	15 (53.57%)	18 (48.65%)	0.694†
Pancreatic disease history			
Acute pancreatitis, n (%)	4 (14.29%)	7 (18.92%)	0.748‡
Chronic pancreatitis, n (%)	2 (7.14%)	4 (10.81%)	1.00‡
Needle			
19 gauge, n (%)	28 (100%)	19 (51.35%)	
22 gauge, n (%)	0	12 (32.43%)	
25 gauge, n (%)		6 (16.22%)	
Cysts location			
Head, n (%)	7 (25.0%)	21 (56.76%)	0.014†
Body, n (%)	8 (28.57%)	5 (13.51%)	0.114‡
Tail, n (%)	9 (32.14%)	3 (8.11%)	0.042‡
Istmo, n (%)	4 (14.29%)	7 (18.92%)	0.748‡
Uncinate process, n (%)	0	1 (2.70%)	
Cyst size, median (range), mm	30 (23.5-35)	23 (18-30)	0.024*
Cyst fluid CEA, median (inter quartile range) (ng/ml)	82 (1.7-582)	71.85 (7.8-292.5)	0.714*
Morphologic features			
Multicystic lesion, n (%)	11 (39.29%)	14 (37.84%)	0.905†
Unilocular, n (%)	17 (60.71%)	22 (59.46%)	0.919†
Septations, n (%)	11 (39.29%)	12 (32.43%)	0.567†
Thickened wall, n (%)	4 (14.29%)	3 (8.11%)	0.453‡
Nodule, n (%)	13 (46.43%)	4 (10.81%)	0.002‡
Liquid features			
Viscous appearance, n (%)	12 (42.86%)	17 (45.94%)	0.524†
Clear aspect, n (%)	17 (60.71%)	23 (63.89%)	0.996†

*Wilcoxon rank test. †Pearson's Chi-squared test. ‡Fisher's exact test. CEA: carcinoembryonic antigen.

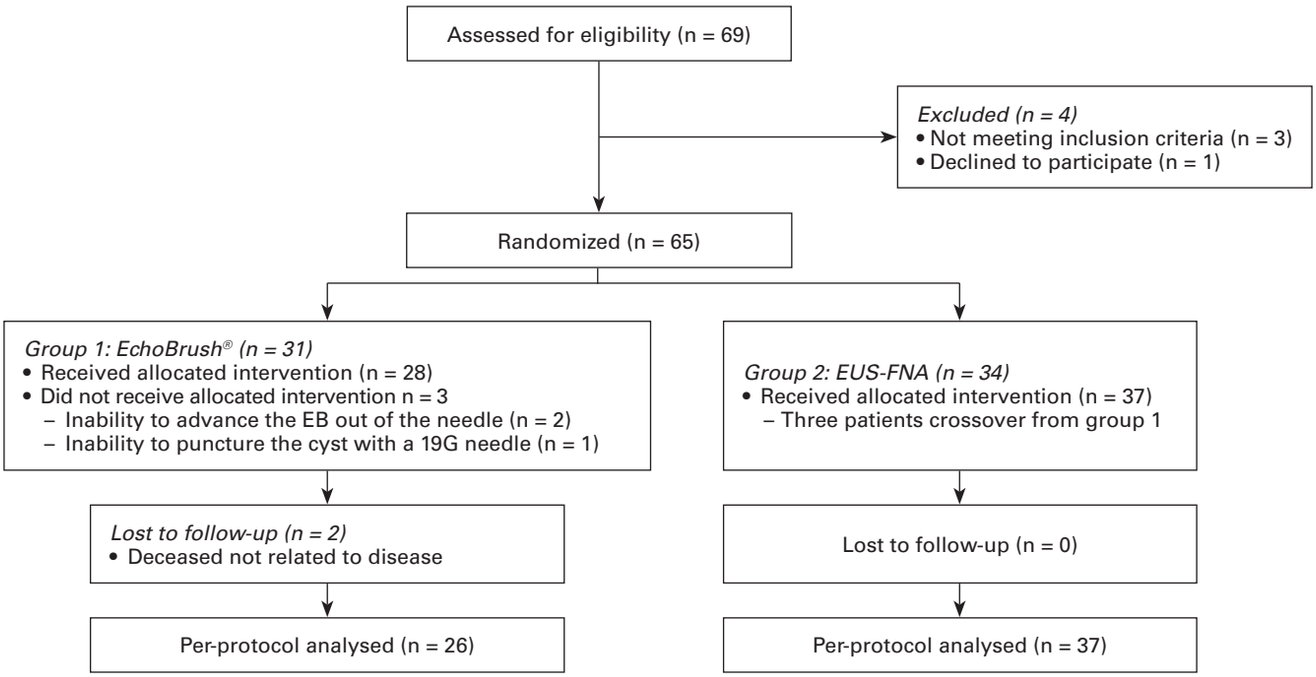

Fig. 2.

EUS-EB group and EUS-FNA group were 50% and 32.4%, respectively.

Diagnostic accuracy of EUS-EB group *vs* EUS-FNA group

The diagnostic accuracy of EUS-EB was not superior to EUS-FNA, neither according to the PP nor to the ITT analysis (38.4% *vs* 45.9%, p = 0.55; and 44.8% *vs* 41.1%, p = 0.77 respectively). Table 2 shows the correlation between cytological diagnosis and histological samples in patients that underwent surgery. No difference between EUS-EB and EUS-FNA was found (p = 0.592).

Diagnostic adequacy of samples in EUS-EB group *vs* EUS-FNA group

The diagnostic adequacy based on the cellularity of samples is shown in table 3 (ITT analysis is shown in supplementary table 3). There was no difference in the diagnostic adequacy of samples between EUS-EB and EUS-FNA (39.3% *vs* 37.8%, p = 0.91; 45.2% *vs* 32.4%, p = 0.29, respectively). However, EUS-EB samples had a greater cellularity than EUS-FNA both according to the PP and ITT analysis.

Table 2. *Correlation between cytological and histological samples*

Case	Technique	Cytological	Histological
1	EUS-FNA	Serous tumor	Serous cystadenoma
2	EUS-FNA	Mucinous tumor	Mucinous cystadenoma
3	EUS-FNA	Indeterminate	Adenocarcinoma
4	EUS-FNA	Mucinous tumor	Mucinous tumor
5	EUS-FNA	Mucinous tumor	Mucinous cystadenocarcinoma
6	EUS-FNA	Indeterminate	Adenocarcinoma
7	EUS-FNA	Mucinous tumor	Neuroendocrine tumor
8	EUS-EB	Mucinous tumor	PanIN
9	EUS-EB	Adenocarcinoma	Adenocarcinoma
10	EUS-EB	Mucinous tumor	Mucinous tumor
11	EUS-EB	Mucinous tumor	Mucinous cystadenoma
12	EUS-EB	Indeterminate	Pseudocyst
13	EUS-EB	Mucinous tumor	Mucinous cystadenocarcinoma

Table 3. *Cellularity of sample (per protocol analysis)*

	High cellularity	Moderate cellularity	Acellular
EUS-EB (n = 28)	4 (14.29%)	7 (25.00%)	17 (60.71%)
EUS-FNA (n = 37)	1 (2.70%)	13 (35.14%)	23 (62.16%)
Total	5 (7.69%)	20 (30.77%)	40 (61.54%)

p = 0.190 (Pearson's Chi-squared test).

Adverse events

There were three adverse events (4.6%), all self-limited intracystic bleeding; one in the EUS-EB group and two in the EUS-FNA group. They were immediately detected during the procedure as a white spot that filled the cyst and did not require any kind of interventional measure. All patients were discharged two hours after the procedure.

DISCUSSION

This multicenter and randomized open-label trial shows that the use of the EchoBrush® does not significantly improve the diagnostic accuracy nor the diagnostic adequacy in the evaluation of CPL in comparison with EUS-FNA. EUS-FNA has been widely used in the diagnosis and work-up of CPL. Cytological evaluation in conjunction with cyst fluid analysis has been performed in an attempt to establish a specific diagnosis when CPL are detected (8). The main goal was the differentiation of mucinous lesions (IPMN and mucinous cystadenomas) from non-mucinous lesions. Several reports have evaluated the sensitivity and diagnostic accuracy of EUS-FNA cytology to detect cancer and mucinous neoplasms with widely varied results (9,10). In a recent prospective study, De Jong et al. obtained a definitive cytopathological diagnosis in only 31% of cases (11). For this reason, some devices have emerged to improve the low yield of EUS-FNA cytology. One of them is the EchoBrush®, a cytology brush designed to use through a 19G EUS needle. This device has shown promising results for improving the diagnostic accuracy of CPL, mainly in the distinction of mucinous lesions (5-7) by improving the cellularity of the sample. Nevertheless, this device has not been compared to EUS-FNA in a randomized manner.

Our results do not show a real benefit of using the EUS-EB instead of EUS-FNA, neither in the ITT analysis nor in the PP analysis. The adequacy of the samples obtained which translates to the diagnostic performance of cytological evaluation was comparable between the two techniques. Furthermore, in some cases it was difficult to puncture a CPL located in the head of the pancreas using EB due to the angulated position of the scope from the duodenum that precluded the use of a 19G needle.

In a previous report, Sendino et al. (5) demonstrated the superiority of the cytobrush specimen *versus* the aspirated fluid in terms of the detection of diagnostic cells and mucinous cells in 30 patients (50%, 95% CI: 31-69% *vs* 18%, 95% CI: 7-38%, p = 0.016). The authors performed both procedures in the same patients; first, aspiration only, and then using the brush. However, there are some serious concerns with regard to this study. There was a high rate of adverse events (10%) and the study was not randomized; in fact, only five lesions were punctured in the head of the pancreas. Due to the high rate of complications, we decided not to aspirate the entire contents of the cyst in order to keep the brush under control the entire time within the cyst.

Al Haddad et al. also reported an initial pilot study (6) and finally a prospective study (which included their previous cases [12]), using the same method as previously described (5). Thirty-nine CPL in 37 patients, with a diameter of over 20 mms. Besides, a high suspicion of mucinous lesions were

evaluated. Cytobrushings were more likely to detect intracellular mucin (and then mucinous lesions) than EUS-FNA (p = 0.001). The rate of adverse events was 8%, including one post-procedure bleeding and two acute pancreatitis. Even though it was a prospective trial, the main critical point was the number of lesions that were punctured in the head of the pancreas (only nine out of 39). Due to the fact that most CPL arise from the pancreatic head, this raises some concerns about the possible selection of the patients. Perhaps cases that imply a difficult approach were excluded from the study. Our results are in concordance with those reported by Thomas et al. (13). This study of 51 patients showed that the diagnostic accuracy of the EchoBrush® was not superior to that of standard EUS-FNA (55% *vs* 61.9%, p = 0.756). Nevertheless, this was neither a prospective nor a randomized trial. The cases were included in two different time periods. A 22G needle was used in the majority of patients in the EUS-FNA group and more than one pass was performed in the same lesion. Furthermore, the rate of adverse events was not reported.

The principal strengths of our study are the six different participating centers that adequately reflect the daily clinical practice for the management of CPL. Furthermore, the randomization of patients and a minimum follow-up of five years that was required to establish the final diagnosis in non-operated cases. This may be a specific problem related to the majority of studies focused on CPL. The lack of surgical specimens and short follow-up periods make the presumptive final diagnosis less reliable.

On the contrary, some limitations must be highlighted. First of all, despite the fact that this was a multicenter trial, not all the centers contributed the same number of patients. Secondly, we took the brush out from inside the needle before aspirating the fluid in order to find out if the friction of the brush against the inner wall of the cyst increased the subsequent cellularity of the sample obtained. Thirdly, there was a small number of patients with a histological diagnosis. Fourth, there was no centralized pathologist that interpreted all the samples and therefore, a bias related to the experience of the cytopathologist cannot be ruled out.

In conclusion, EUS-EB does not improve the diagnostic accuracy nor the diagnostic adequacy in CPL in comparison with the EUS-FNA. New devices and technologies will be required to increase the diagnostic performance of EUS-FNA in this setting.

Supplementary table 1. *Final diagnosis (per protocol analysis)*

	EUS-EB (n = 26)*	EUS-FNA (n = 37)	Total (n = 63)
IPMN, n (%)	10 (38.46%)	20 (54.05%)	30 (47.62%)
Pseudocysts, n (%)	5 (19.23%)	6 (16.22%)	11 (17.46%)
Serous cystadenomas, n (%)	4 (15.38%)	6 (16.22%)	10 (15.87%)
Mucinous cystadenomas, n (%)	3 (11.54%)	1 (2.70%)	4 (6.35%)
Pancreatic adenocarcinoma, n (%)	3 (11.54%)	4 (10.81%)	7 (11.11%)
Panin, n (%)	1 (3.85%)	0	1 (1.59%)

*It was not possible to obtain the final diagnosis in two patients. IPMN: intraductal papillary mucinous neoplasms.

Supplementary table 2. *Cytological diagnosis (per protocol analysis)*

	EUS-EB (n = 28)	EUS-FNA (n = 37)	Total (n = 65)
Inflammatory, n (%)	4 (14.29%)	11 (29.73%)	15 (23.08%)
Serous, n (%)	2 (7.14%)	2 (5.41%)	4 (6.15%)
Mucinous, n (%)	7 (25%)	11 (29.7%)	18 (27.69%)
Pancreatic adenocarcinoma, n (%)	1 (3.57%)	1 (2.70%)	2 (3.08%)
Indeterminate	12 (42.86%)	10 (27.03%)	22 (33.85%)
Inadequate for diagnosis	2 (7.14%)	2 (5.41%)	4 (6.15%)

Supplementary table 3. *Cellularity of sample (intention to treat analysis)*

	High cellularity	Moderate cellularity	Acellular
EUS-EB (n = 31)	4 (12.90%)	10 (32.26%)	17 (54.84%)
EUS-FNA (n = 34)	1 (2.94%)	10 (29.41%)	23 (67.65%)
Total	5 (7.69%)	20 (30.77%)	40 (61.54%)

p = 0.277 (Pearson's Chi-squared test).

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