

Endoscopic Ultrasound–Guided Fine-Needle Aspiration Microhistology in Asymptomatic and Symptomatic Pancreatic Cystic Lesions

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Objective: This study aimed to analyze the usefulness of endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) microhistology to detect malignancy in pancreatic cystic lesions (PCLs).

Methods: Patients with PCLs were identified and submitted to EUS-FNA from January 2010 to January 2017. The percentage of samples suitable for diagnostic classification by microhistology and the positive and negative likelihood ratios to detect malignancy in asymptomatic (APC) and symptomatic (SPC) PCLs were determined.

Results: Endoscopic ultrasound–guided fine-needle aspiration was performed in 510 patients. The resulting material was processed by microhistology and useful for diagnosis in 432 (84.2%). Clinical characteristics of APC (341) and SPC (169) revealed that APC patients were younger ($P = 0.004$) and had smaller PCLs (23 vs 35 mm; $P < 0.001$). In APC, we found more preneoplastic (38.7% vs 30.2%; $P = 0.0016$) and a lower number of malignant PCLs (8.2% vs 24.3%; $P < 0.001$). In APC and SPC, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of microhistology to detect malignancy were 71.4%, 99.7%, 95.2%, 97.5%, and 97.4% ($k = 0.80$) and 58.5%, 96.9%, 85.7%, 87.9%, and 87.6%, respectively.

Conclusions: Endoscopic ultrasound–guided fine-needle aspiration was technically feasible. Microhistology was especially useful to detect neoplastic or malignant PCLs in APC patients.

Key Words: biopsy, fine-needle, endosonography, pancreatic cyst, diagnostic imaging, malignant neoplasms

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The improvement of imaging methods has led to more frequent identification of pancreatic cystic lesions (PCLs).^{1–4} The finding of small pancreatic cysts (including pancreatic pseudocysts [PPs] and retention cysts) in patients with chronic pancreatitis and pancreatic cystic neoplasia represents a dilemma with regard to the therapeutic approach to be adopted.^{5–7} Imaging methods, which rely solely on morphological aspects, are not useful in determining type of PCL or risk of malignancy, especially in lesions <3.0 cm,

even in the presence of associated symptoms.^{8,9} Endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) has also been proposed for diagnosis; however, cyst-fluid cytology is not sufficient to detect malignancy.^{8,9}

In this context, microhistology (McH) may represent a breakthrough in the diagnosis of PCLs. Microhistology provides an accurate diagnosis based on microfragments obtained by EUS-FNA, and thus, it may be useful to determine the appropriate treatment of each case. Reports in the literature that evaluate PCL diagnosis based on EUS-FNA McH are scarce.

The aims of this study were (1) to assess the impact, viability, and safety of EUS-FNA guided tissue acquisition for McH, and (2) to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, and positive and negative likelihood ratios of EUS-FNA McH to detect preneoplastic and malignant features in asymptomatic (APC) and symptomatic (SPC) patients.

MATERIALS AND METHODS

This was an observational study of patients seen at the Endoscopy Sector of Hospital 9 de Julho. Hospital records were searched to select patients with PCLs, who were then prospectively evaluated by EUS-FNA. The study was approved by the Federal University of São Paulo research ethics committee (protocol no. 0344/2018). Informed consent was obtained from all patients.

Patients with PCLs of unknown etiology identified by imaging techniques such as ultrasound, computed tomography, and magnetic resonance cholangiopancreatography/magnetic resonance imaging were included in the study. The presence or absence of PCL-related symptoms (abdominal discomfort, radiating abdominal pain, and difficulty with postprandial gastric emptying) was recorded. Individuals with known coagulation disorders were excluded: prothrombin time >1.5 seconds, partial thromboplastin time >50 seconds, and platelet count <50,000/nL, which would indicate increased risk of bleeding. Individuals with episodes of acute pancreatitis (AP) in the last 6 months before EUS-FNA were also excluded because of the high probability of PP in these cases.

Pancreatic cystic lesions were characterized as epithelial (serous cystadenoma [SCA], mucinous cystadenoma [MCA]), intraductal papillary mucinous neoplasm (IPMN), solid cystic pseudopapillary, mesenchymal (lymphangiomas and teratomas), or presenting secondary cystic degeneration (adenocarcinoma and neuroendocrine tumor).^{8–12}

EUS-Guided Fine-Needle Aspiration

All procedures were performed using a linear Fujinon EG 530UT or EG 530 UT2 endoscopes (FUJIFILM Medical Systems, Wayne, NJ). For FNA, 22G or 19G needles (EchoTip Ultra endoscopic ultrasound needle; Cook Medical, Bloomington, Ind) were used by experienced endoscopists. A 22G needle was used for cysts measuring >0.5 to 2.0 cm in diameter. For cysts ≥2.1 cm,

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regardless of site, a 19G needle was used. Cysts in the pancreatic head and/or the uncinate process were accessed via the duodenum, whereas the body and tail cysts were approached via the stomach.

Pancreatic cystic lesions were preferably punctured with a single pass to minimize the risk of infection. Once the needle was inside the lesion, a 10-mL syringe with vacuum was applied and the contents of the cyst were aspirated, with the needle being moved slowly back and forth through the cyst until no more fluid could be obtained. If solid components were found, they were specifically punctured to obtain a material for McH.^{13,14} In case we obtained little fluid with solid components, we opted always to send the material for McH. During the procedure, a dose of a quinolone-derived broad-spectrum antibiotic was given intravenously. All patients were invariably medicated for another 5 days with the same category of oral antibiotics.

When PCL was identified, the following morphological characteristics were recorded: location, size, cyst multiplicity, type (microcyst, microcyst, or mixed), maximum wall thickness, presence of septa, nodules or calcifications, communication with main pancreatic duct, dilation of main pancreatic duct, and vascular involvement. Reasons for failure to perform FNA included vessels in needle path, strong suspicion of a PP or walled-off necrosis (WON), or confirmation that the supposed PCL was in fact a different anatomical structure.

Cyst Fluid Cytology and McH

Approximately 500 μ L of cyst contents was sent for biochemical analysis (cytology of cystic fluid) whenever possible, for determination of amylase and tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9. Tumor markers and amylase were analyzed by commercially available immunoassays.

The samples obtained by FNA were fixed in 10% formaldehyde (6–24 hours) and subjected to routine processing for the preparation of the specimen and paraffin embedding for McH analysis. Specimens measuring ≥ 1 mm were sent for standard histological processing with paraffin embedding. Samples < 1 mm were sent exclusively for McH processing, along with any residual fixative in the biopsy flasks, for the preparation of tissue blocks with agarose embedding. Such samples and their respective fixatives were centrifuged at 1500 rpm (10'). The supernatant was discarded, and tissue sediment was transferred to Eppendorf tubes, covered with 1.5 mL of 3% agarose, and centrifuged again at 1500 rpm (10').^{13,14} Ancillary histochemical and immunohistochemical methods were used in complex cases for diagnostic definition.

Final Diagnosis

All cases were evaluated by a pathologist specialized in gastrointestinal and pancreatic pathology. The final diagnosis was based on surgical findings and EUS-FNA-guided biopsy.¹⁵

Adverse Events

Adverse events (AEs) are defined as unexpected events associated with morbidity or mortality and occurring during or after EUS-FNA.¹⁶ Adverse events occurring within 2 hours after the procedure were classified as immediate, those occurring within 30 days after were defined as early, and those that occurred after 30 days were classified as late AEs. The severity was defined according to length of hospital stay: mild (< 3 days), moderate (4–10 days), severe (> 10 days), intensive care unit admission, or surgery.¹⁷ Expected AEs were bleeding, AP, infection, and perforation.

The presence or hypothesis of AEs was suggested by clinical, laboratory, and imaging criteria. In some cases, hospitalization or even surgical treatment was indicated based on the evaluation of the teams involved. We asked patients to contact the hospital in

case of abdominal discomfort, pain, or fever. Patients were seen at the outpatient clinic 1 to 2 weeks after the procedure for discussion of the results, investigation of AEs, and decisions about additional management with the respective attending physicians.

Data Collection and Statistical Analysis

Data were presented using descriptive statistics, mean, standard deviation, and minimum and maximum values for quantitative variables and relative percentages for categorical variables. The Shapiro-Wilk test was used to determine normality in the distribution of age and size of PCLs. If normality was not confirmed, the comparisons of these variables between the groups were performed using the Mann-Whitney test. Differences in the distributions of categorical variables such as sex, size, location, and histological type were evaluated with the Pearson χ^2 test. When necessary, Yates continuity correction and Fisher exact test were applied. A significance level of 5% ($P < 0.05$) was used for these analyses.

Microhistology results for the overall group and for APC and SPC were presented in terms of sensitivity, specificity, and PPV and NPV values. The positive and negative likelihood ratios for diagnosis of malignancy were calculated.¹⁸ The conditional probability of having the disease in the presence of a positive test result (positive posttest probability) and the conditional probability of having the disease in the presence of a negative result (negative posttest probability) were calculated from the ratio of joint probabilities of events (intersection) and probability of the conditioning event using the Bayes theorem, where they are presented in Fagan's nomogram.¹⁹

RESULTS

From January 2010 to January 2017, 585 patients underwent diagnostic EUS. For the present analysis, the following were excluded: EUS image suggesting PP and/or WON ($n = 70$); image compatible with cystadenocarcinoma located in the pancreatic body ($n = 1$) or tail ($n = 1$), to prevent seeding; EUS images showing vascular lesion, with positive Doppler signal mimicking PCL ($n = 2$); and duodenal duplication cyst mimicking PCL ($n = 1$).

Thus, 510 (87.1%) of 585 patients were selected, including 351 women (68.8%). There were no technical failures during EUS-FNA for insertion of the needle into the PCL, and acquisition of material for McH was successful in all 510 patients. In addition, sufficient fluid was obtained for biochemical analysis in 297 (58.3%) of 510; in 213 (41.7%) of 510, fluid volume was insufficient or viscosity was too high, so the specimen was only analyzed by McH (Fig. 1).

The clinical characteristics of the overall group as well as those with APC or SPC are described in Table 1. Mean age was 58.2 years, ranging from 11 to 89 years. Abdominal complaints associated with PCL were recorded in 169 (33.2%) patients at the time of presentation; 341 (66.8%) patients had APC. The mean sizes of PCLs in which FNA was performed were 23 mm (range, 2–117 mm) for APC and 35 mm (range, 4–144 mm) for SPC ($P < 0.001$).

A diagnosis was obtained by McH in 432 (84.7%) of 510 patients: 289 (84.7%) of 341 in the APC and 145 (85.7%) of 169 in the SPC group. Biochemical analysis was sufficient for diagnostic classification of PCL in 160 (53.8%) of 297 cases.

Evaluation by a specialized pathologist (F.V.) based on EUS images and laboratory results (amylase, CEA, CA 19-9) classified PCL as benign in 257 (50.6%) patients, as preneoplastic in 184 (35.9%), and as malignant in 69 (13.5%; Table 1). Serous cystadenoma was the most prevalent subtype, with 140 patients (54.2%) followed by simple cyst in 46 patients (17.8%). Pancreatic cystic lesions were associated with von Hippel-Lindau syndrome in 3 patients (1.1%; SCA [1] and SC [2]). In 2 patients (0.7%), PCLs were associated with

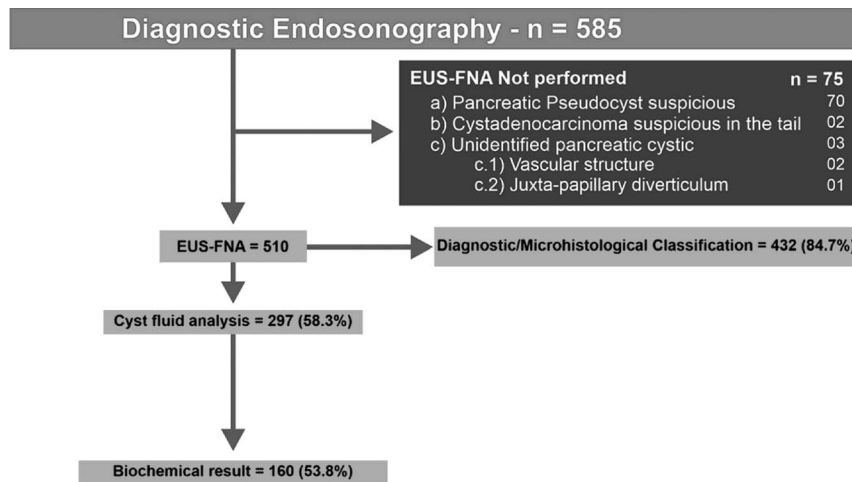


FIGURE 1. Algorithm for patients submitted to EUS-FNA. Results of PCL fluid analysis and McH with EUS-FNA.

pancreatic tuberculosis, and in 1 patient (0.38%), a chronic pancreatitis nodule was found. We also detected PP in 44 (17%) patients, pancreatic intraepithelial neoplasia (PanIN) type 1 in 8 (3.1%), lymphoepithelial cyst in 7 (2.7%), WON in 4 (1.5%), and PanIN-2 in 3 patients (1.1%).

The most common preneoplastic PCLs were IPMN (Fig. 2) in 136 (74.3%) of 184 patients and MCA in 47 (25.7%) of 184 patients. The differentiation between MCA and IPMN was based on histological criteria (eg, presence of ovarian stroma in the sample) or epidemiological characteristics of the patients associated with the results obtained by McH. In 69 patients with

malignancies, IPMN (Figs. 3, 4) was the most prevalent lesion, detected in 19 (27.5%) patients, followed by cystic ductal adenocarcinoma, cystadenocarcinoma, and cystic pancreatic neuroendocrine tumor in 13 patients (18.8%). Solid-pseudopapillary tumor was found in 8 (11.5%) patients, pancreatic cystic lymphoma in 1 (1.4%), and metastasis of cystic renal cell carcinoma in 1 (1.4%). In addition, cancer in situ was diagnosed in 1 patient (1.4%), and PanIN-3 in 1 patient (1.4%). The rates of benign, preneoplastic, and malignant PCLs were 53.1% and 45.6% ($P < 0.001$), 38.7% and 30.2% ($P = 0.016$), and 8.2% and 24.3% ($P < 0.001$) for APC and SPC, respectively (Table 1).

TABLE 1. Clinical Characteristics, Cyst Location, and Cyst Size in Patients With PCLs Undergoing EUS-FNA for McH

Clinicopathologic Factor	Overall Group	APC	SPC	P
No. (%) patients	510 (87.1)	341 (66.8)	169 (33.2)	
Age, mean (range), y	58.2 (11–89)	59.5 (15–86)	55.5 (11–89)	0.004
Sex, female/male	351/159	244/97	107/62	0.059
Site of PCL, n (%)				
Head	262 (52.4)	176 (51.7)	86 (50.8)	0.877
Body	169 (33.1)	116 (34.0)	53 (31.3)	0.548
Tail	43 (8.6)	26 (7.6)	17 (10.0)	0.352
Head/body	17 (3.3)	12 (3.5)	5 (2.9)	
Body/tail	9 (1.8)	5 (1.4)	4 (2.4)	
Head/body/tail	6 (1.2)	3 (0.9)	3 (1.8)	
Head/tail	4 (0.8)	3 (0.9)	1 (0.6)	
Duodenal wall	0	0	0	
Size of PCL, mean (range), mm	27 (2–144)	23 (2–117)	35 (4–144)	<0.001
≤30 mm, n (%)	347 (68)	261 (76.5)	87 (51.4)	
1–10 mm, n (%)	77 (15)	55 (16.1)	22 (13.0)	
11–20 mm, n (%)	149 (29.2)	116 (34.0)	33 (19.5)	
21–30 mm, n (%)	121 (23.7)	90 (26.3)	32 (18.9)	
>30 mm, n (%)	163 (32)	80 (23.5)	82 (48.6)	
31–40 mm, n (%)	66 (12.9)	45 (13.1)	21 (12.4)	
>41 mm, n (%)	97 (19.2)	35 (10.2)	61 (36.0)	
Final diagnosis, n (%)				
Benign	257 (50.6)	181 (53.1)	77 (45.6)	0.399
Preneoplastic	184 (35.9)	132 (38.7)	51 (30.2)	0.016
Malignant	69 (13.5)	28 (8.2)	41 (24.3)	<0.001

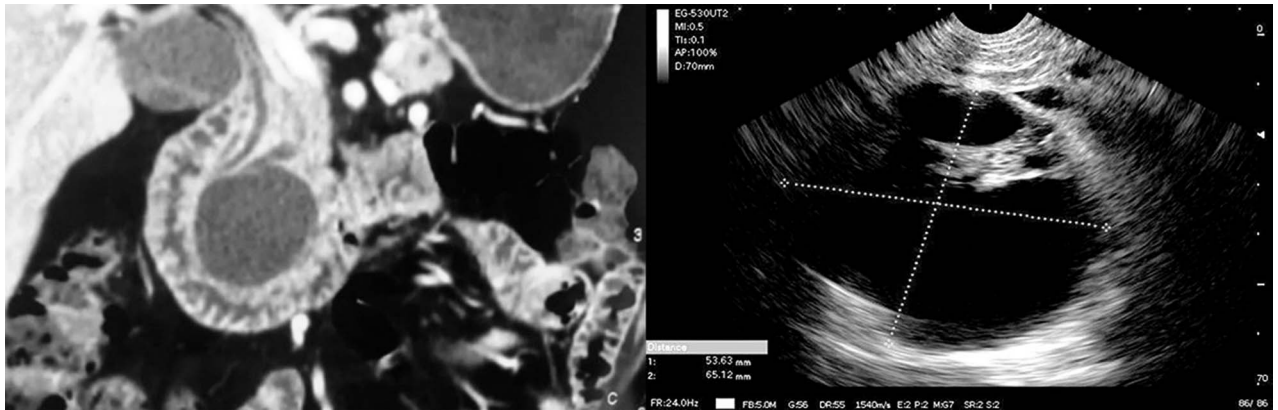


FIGURE 2. A male patient with an AP episode. Computed tomography showed a collection in the pancreatic head (left). Microhistology obtained by EUS-FNA showed IPMN (right). Surgery-confirmed IPMN with superficial cancer.

Considering the final diagnosis, the sensitivity, specificity, PPV, NPV, and accuracy with 95% confidence interval for McH diagnosis of PCL malignancy were 64% (51%–75%), 96% (94%–98%), 71% (60%–83%), 94% (92%–96%), and 92% (89%–94%) respectively. The likelihood ratio and positive and negative posttest probabilities of correct McH diagnosis of PCL malignancy were 62.1% (red line) and 3.6% (green line), for all patients with PCLs (Fig. 5).

Specifically for APC and SPC, McH obtained by EUS-FNA for the diagnosis of PCL malignancy showed sensitivity, specificity, PPV, NPV, and accuracy, with their respective 95% confidence interval, of 71.4% (54%–88%), 99% (99%–100%), 95% (86%–100%), 97% (96%–99%), and 97% (95%–99%), and 59% (46%–70%), 97% (93%–99%), 86% (73%–99%), 88% (82%–93%), and 87% (82%–92%), respectively.

The likelihood ratio and positive (green line) and negative (red line) posttest probabilities for McH detection of APC (Fig. 6) and SPC (Fig. 7) malignancy were 95.7% and 2.8% and 64.9% and 4.1% respectively.

Adverse Events

Twelve (2.3%) immediate AEs occurred, with intracystic bleeding identified by EUS in 3 cases (0.6%). The diagnosis was SCA in 3 cases: 2 presented abdominal pain, which resolved after 48 to 72 hours with rest and symptomatic treatment and without the need for hospitalization, and the other (MCA) had an episode of fever with no clinical repercussions. Eight (1.6%) developed AP (mild in 4, moderate in 2, and severe in 2 cases). In these 8 individuals, PCLs were characterized as IPMN. There were no fatal events in this sample.

DISCUSSION

Pancreatic cystic lesions are classified as mucinous (MCNs) or non-MCNs. The latter are harmless and do not require monitoring; conversely, MCNs have malignant potential and require surgical resection.²⁰ Endoscopic ultrasound has evolved from an imaging technique to become an invasive method that is useful for pancreatic tissue acquisition.²

In this study, EUS-FNA was performed in 510 (87.1%) of 585 patients with PCLs. Microhistology diagnosis was possible in 87.4%, a result quite different from that reported by de Jong et al,²¹ who performed cytological examination in 31% of patients. Our study focused on the sensitivity, specificity, PPV, NPV, and accuracy of McH to identify malignant PCLs, in addition to determining the positive posttest probability for APC and SPC. Two other

studies^{1,22} reported results that were comparable with those of de Jong et al,²¹ with sensitivities of 13% and 35%, respectively, which might be explained by the use of a similar cytology technique in all these studies. In turn, these figures are lower than those reported in another prospective study.²³ Microhistology depends on acquisition of sufficient amount of tissue and on the ability to penetrate the wall of the cyst to get fragments, a different principle from the use of all fluid available as done with biochemical research.^{2,24}

Regarding epidemiology, the present groups were similar to others described in the literature, but there was a statistical difference between APC and SPC. The mean ages were 59.5 and 55.5 years for APC and SPC, respectively ($P = 0.004$). Ferrone et al²⁵ studied 159 APCs and reported location in the head/uncinate process, body, and tail in 60%, 29%, and 11%, respectively. In this study, the head, body, and tail were affected in 51.7%, 34%, and 7.6%, and 50.8% ($P = 0.877$), 31.3% ($P = 0.548$), and 10% ($P = 0.352$) of APC and SPC cases, respectively, without statistical difference. According to the literature, PCLs >3 cm tend to show increased risk of malignancy associated with symptoms.²⁴ This was also the case in our series: the mean size of PCLs was 35 in SPC versus 23 mm in APC, and there was a higher frequency of malignant PCLs in SPC (24.3%) versus APC (8.2%; $P < 0.001$).

Brugge²⁶ studied 247 patients and found that 56% of the lesions were benign. We found benign, preneoplastic, and malignant

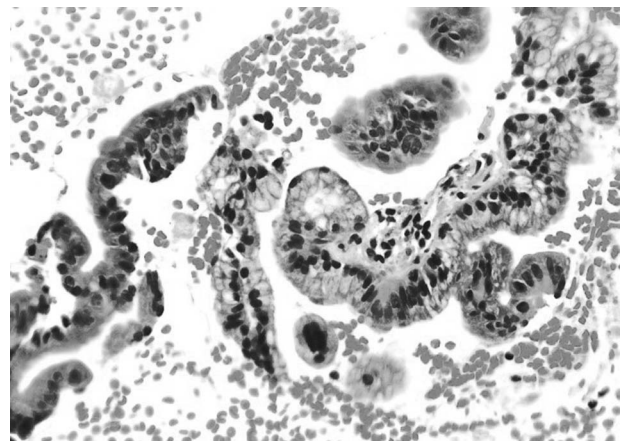


FIGURE 3. An EUS-FNA with McH. IPMN: papillary projections of mucosecretory epithelium with low-grade atypia; hematoxylin and eosin, original magnification $\times 400$.

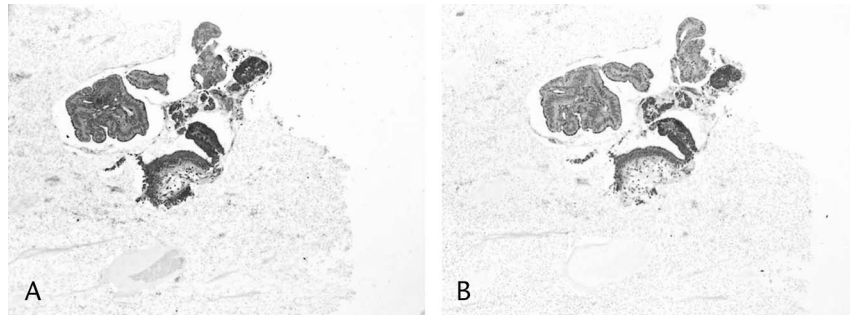


FIGURE 4. A and B, IPMN: papillary projections of mucosecretory epithelium; periodic acid–Schiff positive after diastase digestion, suggestive of IPMN; periodic acid–Schiff without (A) and with (B) digestion, $\times 100$.

PCLs in 50.6%, 35.9%, and 13.5%, respectively. Torresan et al,²⁷ in a study with 87 patients, demonstrated that most PCLs were benign and corresponded to SCA. In our sample, the rates of occurrence of benign, preneoplastic, and malignant PCLs in APC and SPC were 53.1%, 38.7%, and 8.2%, and 45.6%, 30.2%, and 24.3%, respectively. Among benign PCLs, the most frequent finding was SCA (27.4%), followed by SC (9%) and PP (8.6%). In APC and SPC, the number and percentage of SCA, SC, and PP were 39 (23%), 10 (6%), 23 (13%), and 101 (29%), 36 (10%), and 21 (6%), respectively. In the present study, as in the literature,²⁶ SCA was the most prevalent, demonstrating the importance of the diagnosis by McH compared with cytology, which provides low accuracy and sensitivity for this benign type of PCL.^{27–30}

The differentiation between benign, preneoplastic, and malignant PCLs is important because it determines management. Benign APCs do not require treatment, whereas malignant or preneoplastic lesions, in the absence of clinical contraindication, should undergo resection. Endoscopic ultrasound–guided fine-needle aspiration increases the specificity of EUS without impairing sensitivity.³¹ Its accuracy is superior than that of computed tomography and ultrasound-guided biopsy, especially in PCLs <2 cm.³¹ The major concern of percutaneous puncture is the seeding of tumor cells in the path of the needle. In EUS-FNA, the path traveled is shorter, so this complication is rarer.^{32–34}

Endoscopic ultrasound–guided fine-needle aspiration is safe, with few AEs, although perforations and bleeding have been reported.^{31,35} The rate of AEs ranges from 0.3% to 5%. In the present study, the overall rate of AEs was 2.3% (12/510). There were no deaths or cases of infection, and no patient required surgery. Most post-FNA AEs are mild, and the most common AE is AP, as observed in our study. Eight (1.6%) developed mild (4), moderate (2), or severe (2) AP. The 2 patients with severe AP had a final diagnosis of branch duct IPMN. The one with PCL of 2.0 cm was submitted to clinical treatment with good outcome. The other who had a cyst >2.5 cm had an AP episode approximately 1½ years before EUS-FNA. This patient required prolonged hospitalization and percutaneous treatment, but the case turned out well. This rate of occurrence of AEs was comparable with that reported in other studies.^{21,36,37}

Infection of PCLs after FNA is rare, and there is a lack of data to support the use of prophylactic antibiotics, although it is customary practice in most centers.^{31,38} In our series, we believe that no infection occurred, as all PCLs were emptied completely with a single-needle passage. Intracystic hemorrhage is another rare AE, which was described in another study in 6% of cases.³⁹ In our series, this event occurred in 0.6%.

The accuracy and effectiveness of McH in diagnosing APC and SPC had not been determined before. The first study to obtain

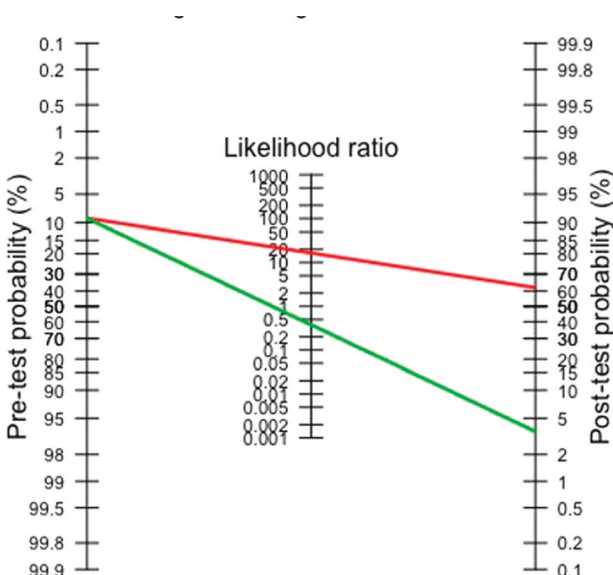


FIGURE 5. Fagan's nomogram in patients with PCLs (510).

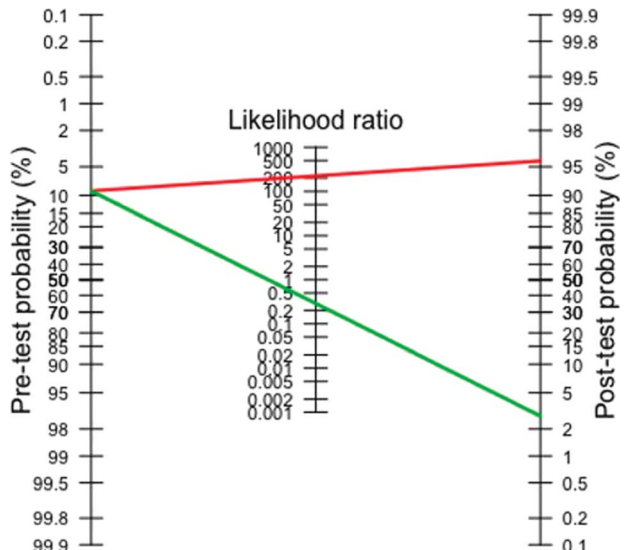


FIGURE 6. Fagan's nomogram in asymptomatic pancreatic cysts (341).

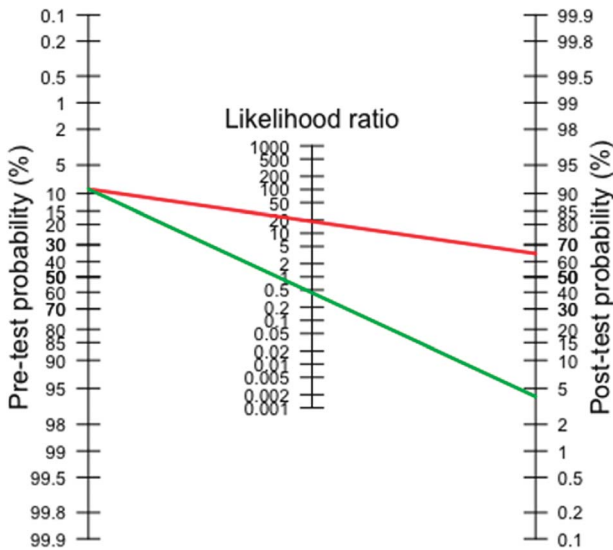


FIGURE 7. Fagan's nomogram in symptomatic pancreatic cysts (169).

a cell block diagnosis using EUS-FNA was that of Mitsuhashi et al,⁴⁰ who diagnosed 91 (80%) of 114 PCLs. Brown et al⁴¹ revealed that cell block analysis increases diagnostic accuracy in up to 14% of patients. Another comparative study between cytology and cell block analysis of histologically confirmed solid and cystic pancreatic tumors showed sensitivity, specificity, PPV, NPV, and accuracy of 61% and 85.2%, 100% and 98.4%, 100% and 93.1%, 36% and 55.1%, and 68% and 86.5% ($P < 0.001$), respectively.¹⁴ With the McH technique, it is possible to increase the accuracy and sensitivity for the material obtained by EUS-FNA to diagnose benign and malignant PCLs.

Despite the extra cost, McH has attracted increasing interest, and new routine implementations of this technique have made it easier to perform, faster, and more cost-effective. Therefore, the use of EUS-FNA with McH as a method in the evaluation and diagnosis of PCLs and differentiation between benign and malignant PCLs as well is justified. In the overall analysis, EUS-FNA with McH had high sensitivity, specificity, and accuracy to diagnose PCLs, allowing for a reliable differential diagnosis. It was not our goal to analyze CEA, CA 19-9, and amylase, although this was possible in 297 (58.3%) patients and conclusive in 160 (53.8%) to differentiate neoplastic from inflammatory PCLs. This was because we chose to send the material for McH evaluation, and in many cases, no fluid was left over for biochemical analysis.

It should be noted that the positive posttest probabilities for patients in the APC and SPC groups were 95.7% and 64.9%, respectively. Considering a prevalence of malignancy of 10% in the population, the probability of an APC patient having the disease given a positive test result was 95.7%, whereas for the SPC patient, the probability of having the disease given a positive test result was 64.9%. These results show that the diagnosis with EUS-FNA was more beneficial in APC versus SPC patients.

To interpret the results of this study, some limitations must be considered. The study was performed in a large cohort of consecutive patients, where the preference was to send the material for McH in formalin. This contrasts with previously published retrospective studies that sent the material for cytology or cell block analysis.^{36,37} Another limitation was the potential selection bias, as the Endoscopy Sector of Hospital 9 de Julho is a national tertiary referral center for this type of examination and diagnosis of pancreatic diseases. In addition, in some patients, FNA was not

performed because of clinical considerations, although the protocol specified FNA performance in all patients. Finally, this study did not evaluate and follow up our cohort of patients in the long term. Long-term monitoring would certainly show the true value of EUS-FNA combined with McH in PCLs, but the present (retrospective) study investigated the technical success and safety of EUS-FNA to obtain specimens for McH and made comparisons between APC and SPC.

In conclusion, EUS-FNA combined with McH in APC and SPC was technically feasible and safe. Microhistology allowed for diagnostic classification of most patients with PCLs, with no difference between APC and SPC. However, APC patients benefited more from McH for the detection of malignant and preneoplastic PCLs compared with SPC.

REFERENCES

1. Brugge WR, Lauwers GY, Sahani D, et al. Cystic neoplasms of the pancreas. *N Engl J Med*. 2004;351:1218–1226.
2. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology*. 2004;126:1330–1336.
3. Irie H, Honda H, Kuroiwa T, et al. Measurement of the apparent diffusion coefficient in intraductal mucin-producing tumor of the pancreas by diffusion-weighted echo-planar MR imaging. *Abdom Imaging*. 2002;27:82–87.
4. Schraibman V, Goldman SM, Ardengh JC, et al. New trends in diffusion-weighted magnetic resonance imaging as a tool in differentiation of serous cystadenoma and mucinous cystic tumor: a prospective study. *Pancreatol*. 2011;11:43–51.
5. Garcea G, Ong SL, Rajesh A, et al. Cystic lesions of the pancreas. A diagnostic and management dilemma. *Pancreatol*. 2008;8:236–251.
6. Sachs T, Pratt WB, Callery MP, et al. The incidental asymptomatic pancreatic lesion: nuisance or threat? *J Gastrointest Surg*. 2009;13:405–415.
7. Kearns M, Ahmad NA. Diagnosis and management of pancreatic cystic neoplasms. *Curr Treat Options Gastroenterol*. 2017;15:587–602.
8. Sarr MG, Kendrick ML, Nagorney DM, et al. Cystic neoplasms of the pancreas: benign to malignant epithelial neoplasms. *Surg Clin North Am*. 2001;81:497–509.
9. Schneider C, Reck T, Greskötter KR, et al. [Cystic pancreatic tumors]. [Article in German]. *Langenbecks Arch Chir*. 1993;378:281–287.
10. Adsay NV, Klimstra DS, Compton CC. Cystic lesions of the pancreas. Introduction. *Semin Diagn Pathol*. 2000;17:1–6.
11. Grieshop NA, Wiebke EA, Kratzer SS, et al. Cystic neoplasms of the pancreas. *Am Surg*. 1994;60:509–514; discussion 514–515.
12. Le Borgne J, de Calan L, Partensky C. Cystadenomas and cystadenocarcinomas of the pancreas: a multiinstitutional retrospective study of 398 cases. French Surgical Association. *Ann Surg*. 1999;230:152–161.
13. Ardengh JC, Lopes CV, de Lima LF, et al. Diagnosis of pancreatic tumors by endoscopic ultrasound-guided fine-needle aspiration. *World J Gastroenterol*. 2007;13:3112–3116.
14. Ardengh JC, Lopes CV, de Lima LF, et al. Cell block technique and cytological smears for the differential diagnosis of pancreatic neoplasms after endosonography-guided fine-needle aspiration. *Acta Gastroenterol Latinoam*. 2008;38:246–251.
15. Mohammad Alizadeh AH, Shahrokh S, Hadizadeh M, et al. Diagnostic potency of EUS-guided FNA for the evaluation of pancreatic mass lesions. *Endosc Ultrasound*. 2016;5:30–34.
16. Johanson JF, Cooper G, Eisen GM, et al. Quality assessment of endoscopic ultrasound. *Gastrointest Endosc*. 2002;55:798–801.

17. Cotton PB. Outcomes of endoscopy procedures: struggling towards definitions. *Gastrointest Endosc.* 1994;40:514–518.
18. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA.* 1994;271:703–707.
19. Fagan TJ. Letter: nomogram for Bayes theorem. *N Engl J Med.* 1975;293:257.
20. Polkowski M, Jenssen C, Kaye P, et al. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline—March 2017. *Endoscopy.* 2017;49:989–1006.
21. de Jong K, Poley JW, van Hooft JE, et al. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. *Endoscopy.* 2011;43:585–590.
22. Attasaranya S, Pais S, LeBlanc J, et al. Endoscopic ultrasound-guided fine needle aspiration and cyst fluid analysis for pancreatic cysts. *JOP.* 2007;8:553–563.
23. Frossard JL, Amouyal P, Amouyal G, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. *Am J Gastroenterol.* 2003;98:1516–1524.
24. Pausawasdi N, Heidt D, Kwon R, et al. Long-term follow-up of patients with incidentally discovered pancreatic cystic neoplasms evaluated by endoscopic ultrasound. *Surgery.* 2010;147:13–20.
25. Ferrone CR, Correa-Gallego C, Warshaw AL, et al. Current trends in pancreatic cystic neoplasms. *Arch Surg.* 2009;144:448–454.
26. Brugge WR. The incidental pancreatic cyst on abdominal computerized tomography imaging: diagnosis and management. *Clin Gastroenterol Hepatol.* 2008;6:140–144.
27. Torresan F, Casadei R, Solmi L, et al. The role of ultrasound in the differential diagnosis of serous and mucinous cystic tumours of the pancreas. *Eur J Gastroenterol Hepatol.* 1997;9:169–172.
28. Carlson SK, Johnson CD, Brandt KR, et al. Pancreatic cystic neoplasms: the role and sensitivity of needle aspiration and biopsy. *Abdom Imaging.* 1998;23:387–393.
29. George DH, Murphy F, Michalski R, et al. Serous cystadenocarcinoma of the pancreas: a new entity? *Am J Surg Pathol.* 1989;13:61–66.
30. Jais B, Rebours V, Malleo G, et al. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). *Gut.* 2016;65:305–312.
31. Balcom JH 4th, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. *Arch Surg.* 2001;136:391–398.
32. Zhu H, Jiang F, Zhu J, et al. Assessment of morbidity and mortality associated with endoscopic ultrasound-guided fine-needle aspiration for pancreatic cystic lesions: a systematic review and meta-analysis. *Dig Endosc.* 2017;29:667–675.
33. Yoon WJ, Daglilar ES, Fernández-del Castillo C, et al. Peritoneal seeding in intraductal papillary mucinous neoplasm of the pancreas patients who underwent endoscopic ultrasound-guided fine-needle aspiration: the PIPE study. *Endoscopy.* 2014;46:382–387.
34. Yamabe A, Irisawa A, Shibukawa G, et al. Rare condition of needle tract seeding after EUS-guided FNA for intraductal papillary mucinous carcinoma. *Endosc Int Open.* 2016;4:E756–E758.
35. Fitzgerald TL, Smith AJ, Ryan M, et al. Surgical treatment of incidentally identified pancreatic masses. *Can J Surg.* 2003;46:413–418.
36. Lee LS, Saltzman JR, Bounds BC, et al. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. *Clin Gastroenterol Hepatol.* 2005;3:231–236.
37. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology.* 1997;112:1087–1095.
38. Klein A, Qi R, Nagubandi S, et al. Single-dose intra-procedural ceftriaxone during endoscopic ultrasound fine-needle aspiration of pancreatic cysts is safe and effective: results from a single tertiary center. *Ann Gastroenterol.* 2017;30:237–241.
39. Varadarajulu S, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc.* 2004;60:631–635.
40. Mitsuhashi T, Ghafari S, Chang CY, et al. Endoscopic ultrasound-guided fine needle aspiration of the pancreas: cytomorphological evaluation with emphasis on adequacy assessment, diagnostic criteria and contamination from the gastrointestinal tract. *Cytopathology.* 2006;17:34–41.
41. Brown KT, Fulbright RK, Avitabile AM, et al. Cytologic analysis in fine-needle aspiration biopsy: smears vs cell blocks. *AJR Am J Roentgenol.* 1993;161:629–631.