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Original Article

Moray Micro Forceps Biopsy Improves the Diagnosis of Specific Pancreatic Cysts

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BACKGROUND: Making a specific diagnosis of pancreatic cysts preoperatively is difficult. The new disposable Moray micro forceps biopsy (MFB) device allows tissue sampling from the pancreatic cyst wall/septum and aims to improve diagnosis. This study compares the diagnostic performance of the MFB with the current conventional analysis of pancreatic cyst fluid (PCF). **METHODS:** A total of 48 patients sampled with MFB were identified. Cysts were classified as mucinous on PCF based on extracellular mucin/mucinous epithelium, carcinoembryonic antigen (CEA) levels ≥192 ng/mL, or *KRAS/GNAS* mutation. A diagnosis of intraductal papillary mucinous neoplasm was supported by *GNAS* mutation; a diagnosis of serous cystadenoma was supported by Von Hippel-Lindau tumor suppressor (*VHL*) mutation. A diagnosis of mucinous cystic neoplasm required the presence of subepithelial ovarian-type stroma. A high-risk cyst was defined as a mucinous cyst with high-grade dysplasia or an adenocarcinoma. Comparisons in diagnostic performance between PCF and MFB were made. **RESULTS:** The mean age of the patients was 69.6 years (range, 27-90 years); 25 of 48 patients (52.1%) were female. Cysts were in the pancreatic head (13 patients), neck (2 patients), body (20 patients), and tail (13 patients), averaging 3.1 cm (range, 1.2-6.0 cm). There was concordance with mucinous versus nonmucinous classification (60.4% for PCF vs 58.3% for MFB; $P = .949$). Three high-risk cysts were detected by PCF and 2 were detected by MFB ($P = .670$). However, MFB diagnosed significantly more specific cysts compared with PCF (50.0% for MFB vs 18.8% for PCF; $P < .001$). **CONCLUSIONS:** PCF analysis and MFB have comparable performance in distinguishing between mucinous and nonmucinous cysts and for detecting high-risk cysts. However, MFB was found to be superior for diagnosing specific cyst subtypes, thus adding significant value to preoperative patient management. ***Cancer Cytopathol* 2018;126:414-20.** © *2018 American Cancer Society.*

KEY WORDS: cyst fluid analysis; Moray micro forceps; mucinous cyst; pancreatic cyst.

INTRODUCTION

Pancreatic cysts are detected by abdominal imaging in up to 13.5% of asymptomatic patients.[1,2] However, the heterogeneity of these cystic lesions in terms of their malignant potential necessitates accurate preoperative diagnosis for proper patient management because pancreatic surgeries are associated with significant morbidity and mortality.[3,4] Currently, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with pancreatic cyst fluid (PCF) analysis is the standard modality for the evaluation of pancreatic cysts,[5–8] with the goal of triaging patients to clinical follow-up versus surgery.

For management purposes, pancreatic cysts first are classified into mucinous versus nonmucinous categories.[7,9] Nonmucinous cysts (ie, pseudocysts, serous cystadenomas) lack malignant potential and usually are managed with observational follow-up. Mucinous cysts are stratified further as low-risk versus high-risk for malignancy, with the latter based on high-risk imaging features (main duct dilatation ≥10 mm, enhancing mural

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TABLE 1. Comparison of Pancreatic Cyst Fluid Analysis and Moray Micro Forceps Biopsy for the Diagnosis of Mucinous Cysts

	No. of Total Cases (%)	*P*1[a]	No. of Cases Measuring <3 cm[b]	*P*2[c]
Diagnostic yield		.818		.750
PCF	35 (72.9)		16 (69.6)	
MFB	36 (75.0)		17 (73.9)	
Mucinous diagnosis		.949		.642
PCF	29 (60.4)		16 (69.6)	
Cytology	26 (89.7)		13 (81.3)	
CEA	13 (44.8)		7 (43.8)	
Molecular	18 (62.1)		9 (56.3)	
MFB	28 (58.3)		15 (65.2)	
High-risk detection		.670		.642
PCF	3 (6.3)		3 (13.0)	
MFB	2 (4.2)		2 (8.7)	
Specific diagnosis		**<.001**		.075
PCF	9 (18.8)		3 (13.0)	
MFB	24 (50.0)		8 (34.8)	

Abbreviations: CEA, carcinoembryonic antigen; MFB, Moray micro forceps biopsy; PCF, pancreatic cyst fluid.
[a] *P* value for all cases. Bold type indicates statistical significance.
[b] N = 23 cases.
[c] *P* value for cases measuring < 3 cm.

nodule ≥5 mm, pancreatic head mass causing obstructive jaundice) and/or high-grade cytology (high-grade atypia [HGA],[10] which encompasses high-grade dysplasia [HGD] or adenocarcinoma). Patients with low-risk cysts undergo clinical surveillance with periodic imaging studies, whereas high-risk cysts prompt resection.

At the current time, PCF analysis at the Massachusetts General Hospital consists of cytology, biochemical analysis with carcinoembryonic antigen (CEA) and amylase levels, and molecular testing via next-generation sequencing (NGS). Cyst fluid CEA (CEA ≥192 ng/mL) has been shown to be the most accurate method for identifying a mucinous cyst, whereas cytology is the best modality for identifying high-risk cysts.[11–13] With the addition of routine molecular analysis, in which *KRAS/GNAS* mutations are highly specific for a mucinous etiology, the detection of mucinous cysts by PCF is reported to have a sensitivity of 90% and a specificity >90%.[14–19]

Although CEA and cytology have relatively high specificity for the detection of mucinous and high-risk cysts, the identification of HGA is difficult and variable between observers,[20] especially when associated with gastrointestinal contamination and/or limited cellularity. Because CEA and molecular mutations do not correlate with grade, a difficult or suboptimal cytology specimen precludes the identification of a high-risk cyst. Furthermore, when draining cyst fluid, subepithelial stroma is not sampled to distinguish mucinous cystic neoplasms (MCNs) from intraductal papillary mucinous neoplasms (IPMNs).

The need for better diagnostic tests for pancreatic cysts has led to the development of through-the-needle miniature biopsy devices for use during EUS-FNA.[21–23] The new Moray micro forceps biopsy (MFB) device (US Endoscopy, Mentor, Ohio) is a disposable tissue procurement device that can be passed through a 19-gauge needle during the endoscopy procedure to sample tissue from the cyst wall and/or septations and allows for the histologic evaluation of architecture and subepithelial stroma.[24] We present what to the best of our knowledge is the first pathology-based study comparing the diagnostic performance of MFB with conventional PCF analysis in the preoperative diagnosis of pancreatic cysts.

MATERIALS AND METHODS

Approval to conduct the current study was obtained from the Massachusetts General Hospital institutional review board. All patients sampled with MFB from January 2016 to September 2017 who had a concurrent cytology specimen were identified. Clinicopathologic information (including patient age, sex, imaging results, PCF analysis, and MFB pathology results) and follow-up information from clinical, operative, and surgical pathology reports were recorded, if available.

The MFB device was introduced through a 19-gauge FNA needle after the cyst fluid was drained, and pinch biopsies of the cyst wall, septations, nodules, or adjacent masses were taken. More than one biopsy was obtained if initial biopsies appeared inadequate macroscopically. The

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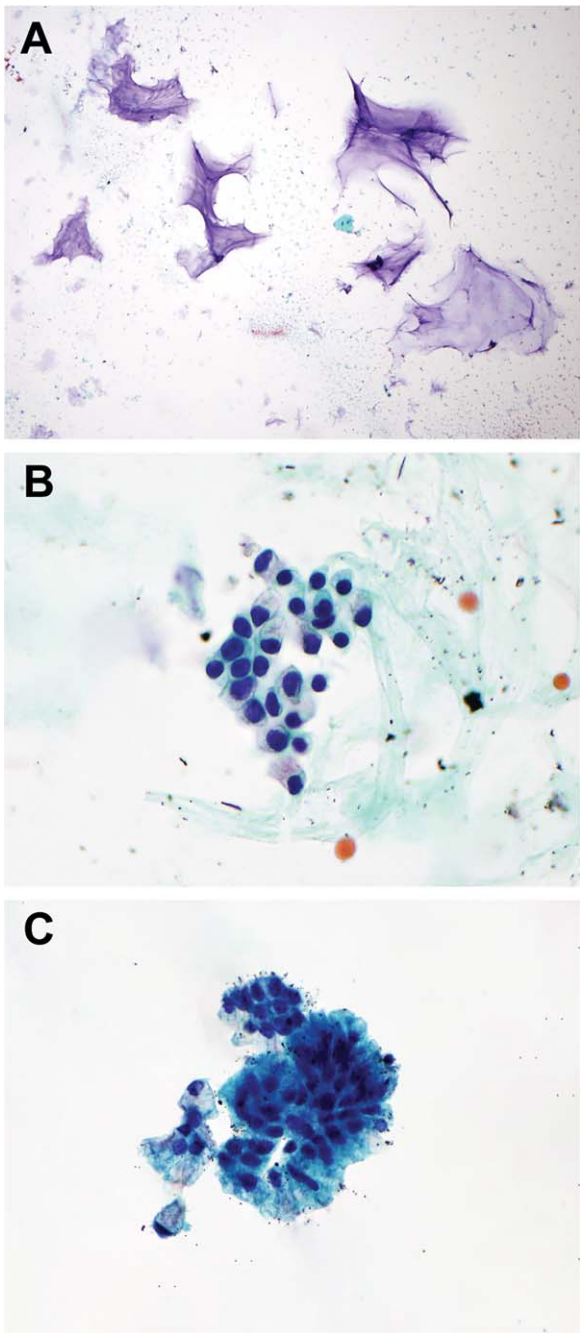

Figure 1. Mucinous features on cytology. (A) Extracellular mucin (Papanicolaou stain, original magnification ×100) and (B-C) mucinous epithelium (Papanicolaou stain, original magnification ×600).

tissue was retrieved from the forceps jaws by shaking the forceps in formalin. Occasionally, the adherent tissue was removed from the forceps with a small sharp stylet.

PCF specimens were processed and triaged in a standardized method,[25] with a portion removed for molecular testing and the remaining cyst fluid spun down as a cytopsin for routine Papanicolaou staining. The supernatant fluid was submitted to the chemistry laboratory for CEA and amylase testing. Molecular analysis was performed using an anchored multiplex polymerase chain reaction NGS platform.[26]

Cysts were classified as mucinous by PCF analysis based on the presence of extracellular mucin or mucinous epithelium on cytology, a CEA level ≥192 ng/mL, and/or a *KRAS* or *GNAS* mutation. On PCF analysis, a specific diagnosis of IPMN was supported by a *GNAS* mutation, and a specific diagnosis of serous cystadenoma (SCA) was supported by a Von Hippel-Lindau tumor suppressor (*VHL*) (3p25) mutation. On MFB, cysts were classified as mucinous by the presence of mucinous epithelium; a specific diagnosis of MCN required the presence of subepithelial ovarian-type stroma. A high-risk cyst was defined as a mucinous cyst with HGA, HGD, an adenocarcinoma, or a cystic neuroendocrine tumor.

Statistical Analysis

Continuous variables were compared using 2-sided Student *t* tests and categorical variables were assessed using the Fisher exact test. *P* values <.05 were considered to be statistically significant. Statistical analyses were performed using R statistical software (version 3.2.2; R Foundation, Vienna, Austria).

RESULTS

A total of 48 cases with concurrent PCF and MFB specimens formed the study cohort. The mean age was 69.6 years (standard deviation, 11.1 years) with a range of 27 to 90 years; 52.1% of the patients were female (25 of 48 patients). Cysts were located in the pancreatic head (13 patients; 27.1%), neck (2 patients; 4.2%), body (20 patients; 41.7%), and tail (13 patients; 27.1%). The average cyst size was 3.1 cm (standard deviation, 1.1 cm), with a range of 1.2 to 6.0 cm. There were no major complications from the MFB procedure.

Comparing the diagnostic performance of PCF analysis with that of MFB, there was no significant difference noted with regard to diagnostic yield (72.9% for PCF vs 75.0% for MFB; $P = .818$), and there was concordance with the classification of mucinous versus nonmucinous etiology (60.4% for PCF vs 58.3% for MFB; $P = .949$) (Table 1). Of the 29 cysts classified as mucinous by PCF analysis, 26 (89.7%) had mucinous features on cytology:

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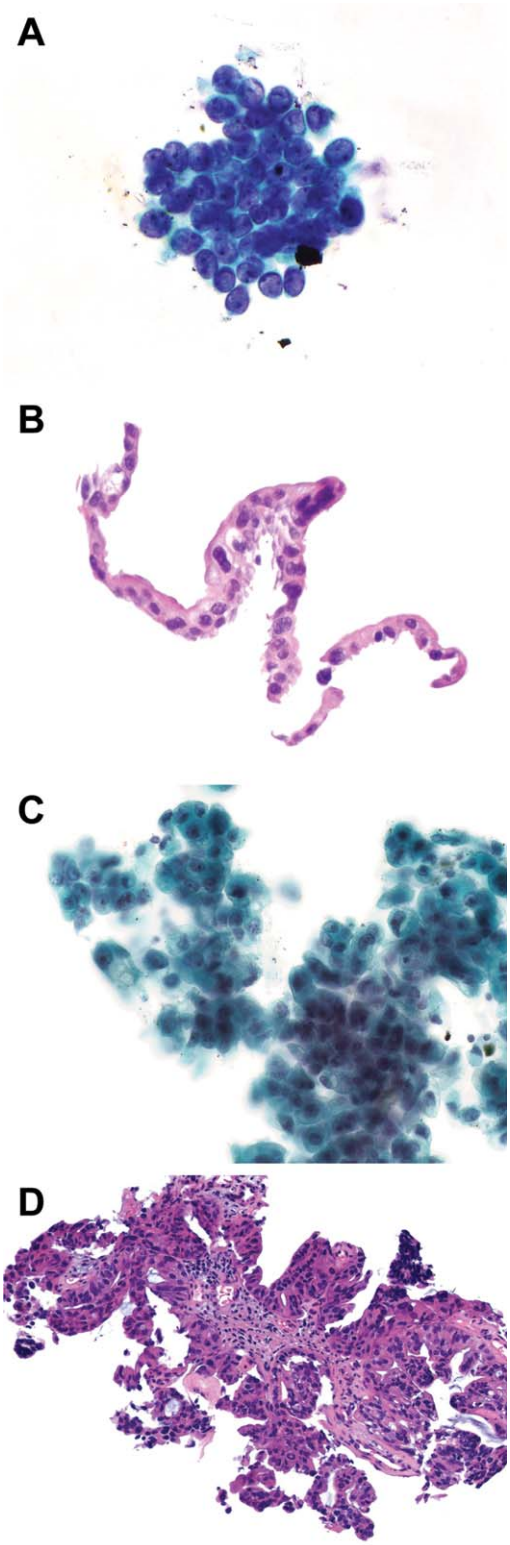

Figure 2. Mucinous epithelium with (A) high-grade atypia on cytology (Papanicolaou stain, original magnification ×600) and (B) high-grade dysplasia on Moray micro forceps biopsy (H & E, original magnification ×400). Adenocarcinoma on (C) cytology (Papanicolaou stain, original magnification ×600) and (D) Moray micro forceps biopsy (H & E, original magnification ×400).

TABLE 2. Specific Cysts Diagnosed by Pancreatic Cyst Fluid and Moray Micro Forceps Biopsy

	No. of Cases (%)
PCF	
IPMN-LGA	6 (12.5)[a]
Adenocarcinoma	1 (2.1)[b]
SCA	2 (4.2)[c]
MFB	
IPMN-LGD	18 (37.5)
MCN	1 (2.1)
Adenocarcinoma	1 (2.1)
Acinar cell cystadenoma	1 (2.1)
SCA	3 (6.3)

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; LGA, low-grade atypia; LGD, low-grade dysplasia; MCN, mucinous cystic neoplasm; MFB, Moray micro forceps biopsy; PCF, pancreatic cyst fluid; SCA, serous cystadenoma.
[a] All cases diagnosed by *GNAS* mutation (IPMN) and cytology (LGA).
[b] Diagnosed by cytology alone.
[c] One case was diagnosed by cytology alone and one case was diagnosed by *VHL* (3p25) mutation.

13 of 29 cysts (44.8%) had extracellular mucin, 20 of 29 cysts (69.0%) had mucinous epithelium, and 8 of 29 cysts (27.6%) demonstrated both features (Fig. 1). In addition, 13 of 29 cysts (44.8%) had a CEA level ≥192 ng/mL. The average CEA level among mucinous cysts was 669.5 ng/mL compared with 12.4 ng/mL among nonmucinous cysts ($P = .003$). The average PCF amylase level was not found to be significantly different between mucinous and nonmucinous cysts (35,845 U/L vs 37,319 U/L; $P = .953$).

NGS was positive for a significant mutation in 18 of 48 cases (37.5%); molecular testing was not performed in 5 cases (10.4%), and there was insufficient material for analysis in another 15 cases (31.3%). Mutations in *KRAS*, *GNAS*, and both *KRAS* and *GNAS* were detected in 11 cases (22.9%), 2 cases (4.2%), and 4 cases (8.3%), respectively, supporting a mucinous classification in 17 PCF cases. The last relevant mutation was a *VHL* mutation detected in 1 PCF, which supported a diagnosis of SCA. Other observed mutations included *MSH2, ERBB4, BRCA2, ARID1A, ATM,* and *TP53* (1 each).

Three high-risk cysts were detected by PCF (2 mucinous cysts with HGA and 1 adenocarcinoma) and 2 were detected by MFB (1 mucinous cyst with HGD and 1 adenocarcinoma) ($P = .670$) (Fig. 2). However, MFB diagnosed significantly more specific cysts compared with PCF (50.0% for MFB vs 18.8% for PCF; $P<.001$) (Table 2). Both PCF analysis and MFB could detect IPMNs with low-grade atypia/dysplasia (Fig. 3), adenocarcinoma (Fig. 2), and

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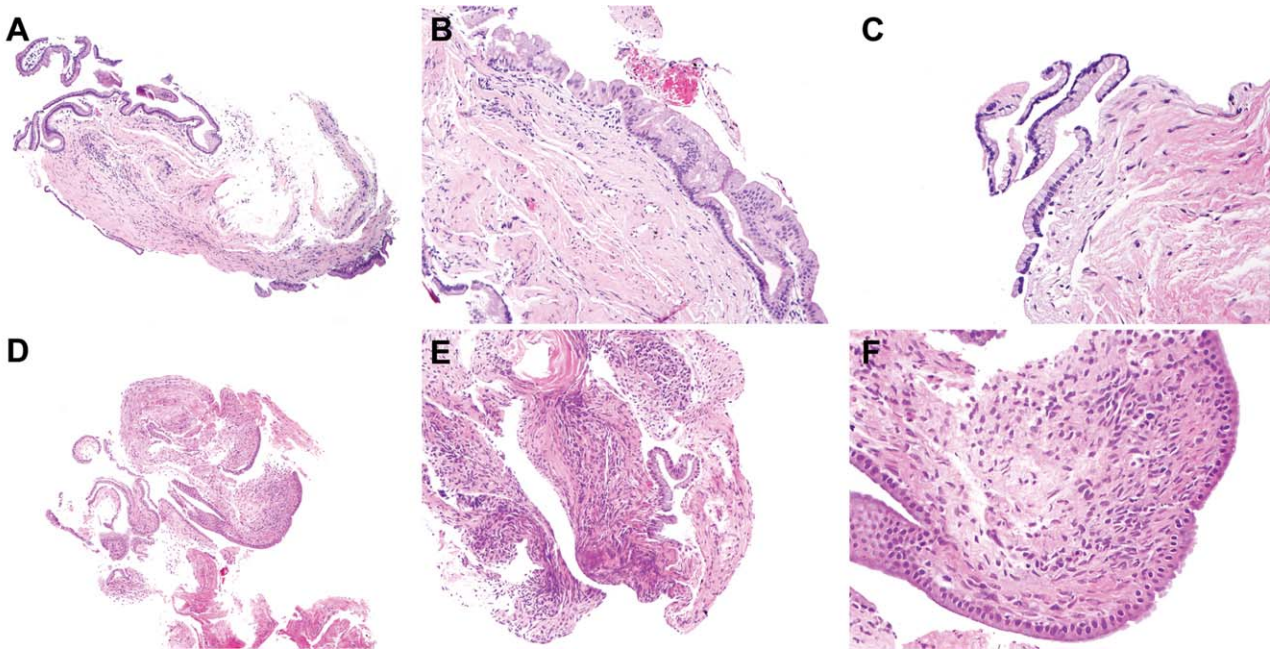

Figure 3. H & E staining of Moray micro forceps biopsy of intraductal papillary mucinous neoplasm at (A) original magnification ×100, (B) original magnification ×200, and (C) original magnification ×400, and of mucinous cystic neoplasm at (D) original magnification ×100, (E) original magnification ×200, and (F) original magnification ×400.

SCAs (Fig. 4). However, 3 times as many IPMNs, 1 MCN (Fig. 3), and 1 acinar cell cystadenoma[27] were diagnosed by MFB alone.

When stratifying by cysts <3 cm in size (23 cysts), the diagnostic yield, detection of mucinous cysts, and detection of high-risk cysts remained comparable between PCF analysis and MFB (Table 1). Among these cysts, MFB diagnosed marginally significantly more specific cysts versus PCF (34.8% for MFB vs 13.0% for PCF; $P = .075$).

On follow-up, 37 patients remained under surveillance, 9 patients underwent surgical resection, 1 patient received chemotherapy due to metastatic adenocarcinoma, and 1 patient died of other medical comorbidities. Surgical pathology follow-up was available for 10 cases (9 resection specimens and 1 biopsy specimen) and demonstrated concordance with the PCF/MFB diagnosis, except in 2 cases in which the PCF/MFB results were nondiagnostic (Table 3).

DISCUSSION

Despite optimization of PCF analysis using a multimodal approach combining cytology and ancillary testing for the preoperative diagnosis of pancreatic cystic lesions,[8,15] it remains challenging to properly risk stratify patients for expectant versus surgical management. Furthermore, in the majority of cases, a specific diagnosis can only be confidently diagnosed by PCF analysis if a *GNAS* mutation (for IPMN) or *VHL* mutation (for SCA) is detected by molecular analysis. The new MFB device allows for simultaneous tissue sampling from the pancreatic cyst wall/septae during the EUS-FNA procedure, thus providing a histologic sample in addition to PCF.

To our knowledge, this is the first pathology-based report regarding the performance of MFB. In the current study, we demonstrated that PCF analysis and MFB have comparable diagnostic performance in terms of diagnostic yield (>70%), diagnosis of mucinous cysts, and detection of high-risk cysts. However, MFB was superior in diagnosing specific cyst types and allowed for the diagnosis of 2.7 times as many specific cysts as PCF analysis among all cysts and those measuring <3 cm in size.

Differentiating between certain specific cysts has important implications for management. SCAs of the pancreas are benign lesions that do not require any intervention unless the patient is symptomatic from mass effect. However, previous studies have shown that serous epithelial cells were identified in <20% of cases on EUS-FNAs[28] and that a cytological diagnosis of SCA was made in only 10% of cases with subsequent surgical pathology

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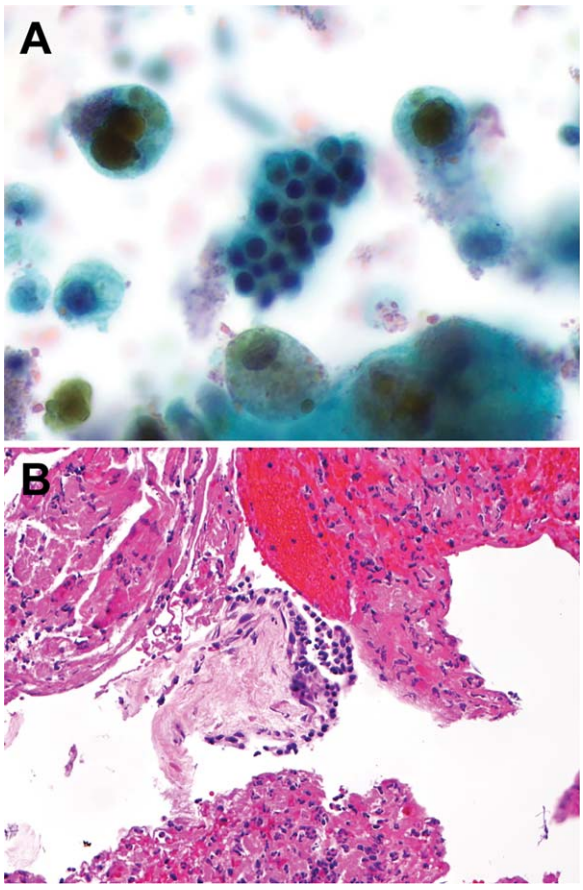

Figure 4. Serous cystadenoma on (A) cytology (Papanicolaou stain, original magnification ×600) and (B) Moray micro forceps biopsy (H & E, original magnification ×400).

confirmation.[29] Using PCF analysis, we found 2 cases diagnosed as SCA: 1 by serous epithelial cells on cytology and 1 through detection of a *VHL* mutation. However, using MFB alone, we were able to identify 3 cases with serous epithelium, thus facilitating a more accurate and reliable preoperative diagnosis of SCA.

It is also important to distinguish MCN from IPMN, a distinction that is challenging by cytology because the subepithelial stroma is not sampled; the presence of subepithelial ovarian-type stroma is a defining characteristic of MCNs. Branch duct IPMNs without high-risk features behave in a benign fashion and occur mostly in elderly patients, thereby supporting a conservative management approach.[7] In contrast, surgical resection is recommended for all surgically fit patients with MCNs because they are premalignant lesions that tend to occur in a younger population, and their location in the body/tail of the pancreas lends them to less morbid distal pancreatectomy or laparoscopic procedures. In the current study,

TABLE 3. Cysts With Histological Follow-Up

Case No.	PCF/MFB Diagnosis	Surgical Pathology Diagnosis
1	Serous cystadenoma	Serous cystadenoma
2	Mucinous-HGD	Adenocarcinoma arising from MD-IPMN
3	Adenocarcinoma	Adenocarcinoma arising from IPMN-HGD
4	Mucinous-LGD	MD/BD-IPMN-LGD
5	Nondiagnostic	Mucinous cystic neoplasm-LGD
6	Acinar cell cystadenoma	Acinar cell cystadenoma
7	Nondiagnostic	Adenocarcinoma[a]
8	IPMN-LGD	BD-IPMN-LGD
9	Mucinous-LGD	Mucinous cyst-LGD, possibly IPMN
10	Mucinous-LGD	MD/BD-IPMN-LGD

Abbreviations: BD, branch duct; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD, main duct; MFB, Moray micro forceps biopsy; PCF, pancreatic cyst fluid.
[a] Biopsy only; patient had metastatic disease.

we found only 6 IPMNs diagnosed on PCF, all by *GNAS* mutation. MFB diagnosed 3 times as many IPMNs through the presence of mucinous epithelium and a lack of subepithelial ovarian-type stroma, as well as 1 MCN through the identification of subepithelial ovarian-type stroma. The distinction between these 2 types of mucinous cysts was only possible with the addition of MFB.

No major complications were reported with this patient cohort. From our overall experience, there are 2 types of complications with MFB: local bleeding from the biopsy site and pancreatitis. Bleeding usually is self-limited and does not result in any symptoms. Pancreatitis caused by passage of the needle through pancreatic parenchyma is a rare and mild complication, occurring in approximately 10% of patients.

The limitations of the current study include the relatively small number of cases sampled with MFB. In addition, molecular results were not available in approximately 40% of cases and surgical pathology follow-up was only available in approximately 20% of cases, making it difficult to evaluate the true rate of accurate diagnoses by PCF analysis and MFB. Nonetheless, the results of the current study demonstrated the superior performance of MFB in diagnosing specific cyst types and its significant additional contributions to the preoperative diagnosis and management of pancreatic cysts.

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CONFLICT OF INTEREST DISCLOSURES

William R. Brugge has accepted a funded grant for collecting research on pancreatic cystic lesion biopsies outside of the current study. Martha B. Pitman has acted as a paid consultant for Medtronic Inc and Boston Scientific Inc for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

M. Lisa Zhang: Conceptualization, data curation, formal analysis, investigation, methodology, writing-original draft, and writing-review and editing. **Ronald N. Arpin**, **William R. Brugge**, **David G. Forcione**, and **Omer Basar**: Data curation and writing-review and editing. **Martha B. Pitman**: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, and writing-review and editing.

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