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Factors affecting the diagnostic value of liquid-based cytology by EUS-FNA in the diagnosis of pancreatic cystic neoplasms

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ABSTRACT

Background and Objectives: This study retrospectively evaluated the value of liquid-based cytology (LBC) alone for diagnosing pancreatic cystic neoplasms (PCNs) in a large sample and initially estimated factors that might affect LBC diagnostic ability.

Methods: From April 2015 to October 2022, we prospectively enrolled 331 patients with suspected PCNs in our prospective database. Among them, 112 patients chosen to receive surgical resection were included. Only 96 patients who underwent EUS-guided cystic fluid LBC were finally studied. The diagnostic values of LBC for differentiating benign and malignant PCNs and subtypes of PCNs were evaluated.

Results: There were 71 female and 25 male patients with a mean age of 47.6 ± 14.4 years. The median cyst size was 43.4 mm. The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of LBC for the differentiation of benign and malignant PCNs were 96.9%, 57.1%, 100%, 100%, and 96.7%, respectively. The overall diagnostic accuracy of LBC for specific cyst types was 33.3% (32/96). Cysts located in the pancreatic body/tail or with irregular shapes were more likely to obtain a definite LBC diagnosis. At the same time, age, sex, tumor size, cystic fluid viscosity, operation time, needle type, and presence of septation were not significantly different.

Conclusion: Liquid-based cytology alone is useful for differentiating benign PCNs from malignant PCNs and can successfully characterize the PCN subtypes in one-third of patients. Pancreatic cystic neoplasms located in the body/tail or exhibiting irregular shapes are more likely to obtain a definite LBC diagnosis.

Key words: Cystic fluid; EUS; Liquid-based cytology; Pancreatic cystic neoplasms

INTRODUCTION

With the increasing awareness of health examinations and their development, there are more pancreatic cystic lesions (PCLs) demonstrated by abdominal imaging techniques. The incidence of PCLs at autopsy was reported to be as high as 24%.[1] The incidence of PCLs increased with age and may rise to 25% in individuals older than 70 years.[2] Pancreatic cystic lesions are mainly divided into nonneoplastic and neoplastic cysts, and the latter cysts should be given more attention for their possibility of malignant transformation. Neoplastic cysts, namely, pancreatic cystic neoplasms (PCNs), mainly consist of several common types, including serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intraductal papillary neoplasms (IPMNs), and solid pseudopapillary neoplasms (SPNs).[3] Malignancy varies with the types of PCNs. Nonmucinous cysts, namely, SCNs, are considered benign. Serous cystic neoplasms can be surveilled for those without worrisome features under EUS, and EUS-guided ablation also can be used in SCNs in cases of abrupt size increase and of tumors larger than 3 cm.[4] Mucinous cysts, namely, MCNs and IPMNs, are believed to be premalignant. Intraductal papillary neoplasm is a type of cystic tumor with obvious heterogeneity and malignant potential. The risk of malignant transformation of different types of IPMNs varies greatly. At present, there are still great controversies about its surgical indications and surgical options. For patients with MCNs who have no obvious malignant features and do not require surgical intervention, EUS-guided ablation could be considered.[5,6] Solid pseudopapillary neoplasms are recommended to be resected for their low-grade malignancy. Treatment methods depend on the diagnosis of the subtypes of PCNs. The prognosis of PCNs will decrease severely if they develop into pancreatic cancer. Therefore, discrimination of PCNs from other PCLs and exact diagnosis of the subtypes of PCNs are of great importance for planning the further management and prognosis of patients with PCNs.

Imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), were most frequently used to diagnose pancreatic lesions. However, their diagnostic accuracy was not satisfactory, especially regarding the ability to characterize PCNs.[7,8] The accuracy of MRI was revealed to be 55% to 76% and 40% to 50% for differentiating benign from malignant cysts and diagnosing the specific type of PCNs, respectively.[9] EUS can provide higher-resolution images with dynamic videos. EUS was believed to provide visualization of the detailed structures of PCNs and to diagnose the subtypes of PCNs better than CT and MRI

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can.[10] Although the sensitivity of cytology is low, EUS-FNA has been regarded as the most valuable technique for distinguishing benign PCNs from malignant PCNs and characterizing the PCN subtypes.[11] It can obtain cystic fluid for cytologic, biochemical, and tumor marker analysis.[11,12] Biochemical analysis mainly included amylase and lipase levels. A cutoff of 250 U/L was regarded as the most valuable for distinguishing pseudocysts and IPMNs from SCNs, MCNs, and SPNs.[13] Carcinoembryonic antigen (CEA) was the most common tumor marker compared with other tumor markers during cystic fluid analysis, with an optimal cutoff of 192 ng/mL for differentiating mucinous and nonmucinous cystic lesions.[14–16] Brugge et al[14] reported that CEA functions better than EUS morphology and cytology, and no combination of tests was found to provide higher accuracy than CEA alone. However, the latest studies demonstrated that combination parameters ensured the best results for accuracy, which could be as high as 90%.[17–19] Low cyst fluid glucose, a new potential biomarker, was demonstrated to be helpful to improve the diagnostic accuracy compared with CEA alone for the differentiation between mucinous and nonmucinous PCLs.[20,21]

In recent years, new techniques have been introduced to improve diagnostic accuracy, such as EUS-guided fine-needle biopsy, EUS-guided through-the-needle biopsy, and EUS-guided needle-based confocal laser endomicroscopy.[22–28] However, these techniques have not been well accepted for several reasons, for example, the inability to obtain sufficient cystic wall tissue to give a positive pathologic diagnosis, significant difficulty in operation, or failure to provide a distinct image. EUS-FNA is still regarded as the optimum diagnostic method for PCNs. Cytology was regarded as the central part of the cystic fluid analysis.[29] Many studies have revealed the diagnostic value of EUS-FNA[7,30–32]; however, few investigations have focused on the diagnostic value of EUS-guided cystic fluid liquid-based cytology (LBC), especially for the diagnosis of PCNs.[13,33–37] Moreover, no study has evaluated the factors determining the diagnostic value of cystic fluid LBC analysis by EUS-FNA in differentiating benign and malignant PCNs and different types of PCNs. Therefore, our present study retrospectively evaluated the value of LBC alone in diagnosing PCNs in a large sample and initially evaluated the factors that might affect the diagnostic ability of LBC.

PATIENTS AND METHODS

Study design

From April 2015 to October 2022, we prospectively enrolled 331 patients suspected of PCNs in our "diagnosis and treatment of PCNs study" database. After excluding patients receiving imaging follow-up and EUS-guided lauromacrogol ablation (EUS-LA), we retrospectively chose 112 patients who underwent surgical resection from this prospective database. Data of only 96 patients who underwent EUS-guided cystic LBC were studied after excluding those of 16 patients without EUS, EUS-FNA, or cytological analysis. This study was approved by the institutional review board of Chinese PLA General Hospital and registered in the Chinese Clinical Trials Registry (no. ChiCTR-OOC-15006118).[38]

EUS procedure

Before EUS, imaging techniques such as abdominal ultrasound, CT, and MRI were recommended for patients with suspected PCNs. EUS evaluation was performed mainly by 3 experienced experts with experience in more than 100 cases of EUS. Patients were placed in the left-lateral position under intravenous anesthesia. First, EUS (Prosound F75 [Aloka, Tokyo, Japan] and GF-UCT260 [Olympus, Tokyo, Japan]) was performed to evaluate the morphology of the lesions. Then, Doppler imaging was used to identify the blood supply of the lesions. Third, contrast-enhanced EUS was performed to further evaluate the cyst with the injection of 4.8 mL of SonoVue (Bracco Suisse SA, Plan-les-Ouates, Switzerland) through the anterior elbow vein. Fourth, the optimum puncture point and path were chosen to perform transgastric or transduodenal puncture via a 19- or 22-gauge Echotip needle (Cook, Limerick, Ireland). Cystic fluid was aspirated and sent for cytologic, biochemical, and tumor marker analysis. Finally, the needle was withdrawn, and the puncture point was carefully evaluated to rule out active bleeding. SpyGlass fiber-optic probes (SpyGlass 4603, SpyGlass Lightsource 4619, and SpyGlass Camera 4610; Boston Scientific, Natick, MA) were used to inspect the intracystic wall and contents to provide more helpful information for final diagnosis in selected cases in which primary diagnosis under EUS was difficult to make.[3] SpyGlass was inserted into the cystic cavity through a 19-gauge needle in 58 of 96 patients.

Cytologic examination

We assessed the blood supply around the cyst by EUS to look for the optimal puncture site, and then the stomach wall or duodenal wall was punctured with a 19- or 22-gauge needle, pierced through the cyst wall and entered the cyst cavity. We used syringe to collect the cystic material by negative-pressure aspiration. If the cystic fluid was too viscous and difficult to aspirate, the cyst fluid could be diluted by injecting normal saline into the cyst cavity, recording the volume of normal saline, and calculating the dilution factor. It was considered to use a 19-gauge needle to replace 22-gauge for a thicker aperture. Finally, the cystic material was injected into a single vial that contained a liquid-based fixation medium with a volume of 20 mL (Cytyc Corporation, Boxborough, MA). If the cystic fluid was sufficient, more than 3 mL of this fluid was injected for LBC analysis. Before that, a few milliliters of the liquid-based fixation medium were aspirated to leave space for cystic fluid. The vial was sent to the pathological laboratory to prepare a thin monolayer of cells. Two cytopathologists were assigned to make a diagnosis. The final diagnosis was made when they reached an agreement.

Postprocedure treatment

Patients fasted on the operation day. An intravenous antibiotic was used for 0 to 3 days. A proton-pump inhibitor (PPI) and octreotide were intravenously administered on the operation day, and blood tests were performed to evaluate the serum amylase level on the first morning after the operation. If it was normal and discomfort was not complained by patients, intravenous PPI and octreotide were stopped, followed by oral PPI therapy for 3 to 7 days.

Definition

The cytologic diagnosis was regarded as malignant if the report demonstrated definite malignancy or suspicion of malignancy. The cytologic diagnosis was considered benign if the report revealed benign cytology or no sign of malignant cells. If the report indicated a mucinous cyst, we defined it as MCN, instead of IPMN, without taking EUS imaging into consideration.

Pathology obtained from surgically resected specimens was regarded as the criterion standard. The malignant cysts included cystadenocarcinoma, neuroendocrine neoplasm (NEN), and cysts with high-grade dysplasia. Benign cysts were defined as follows: (1) diagnosis of SCN, MCN, IPMN, and SPN without malignant signs or with low- or intermediate-grade dysplasia and (2) other benign cysts, such as true cysts and pseudocysts.

The period between fine-needle injection and the withdrawal of the needle was calculated as the operation time. We regarded the time used in EUS-FNA as the operation time and did not take the time spent in EUS evaluation into consideration.

Statistical analysis

SPSS version 26.0 statistical software (IBM Corp, Armonk, NY) was used for statistical analysis. Quantitative variables, including age, size, and operation time, were described as the mean ± SD or the median (ranges) and were assessed by Student *t* test or a nonparametric test according to distribution characteristics. Categorical variables, including sex, location, shape, needle type, and diagnosis, were expressed as frequencies and assessed using Fisher exact test or the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

From April 2015 to July 2022, we prospectively enrolled 331 patients suspected of having PCNs in our database. A total of 112 patients who underwent surgical resection were retrospectively enrolled from this prospective database. After excluding 16 patients without EUS ($n = 4$), EUS-FNA ($n = 8$), or cytology analysis ($n = 4$), 96 patients who underwent EUS-guided cystic fluid LBC were finally enrolled. There were 71 female and 25 male patients with a mean age of 47.6 ± 14.4 years. The median size of the cyst was 43.4 mm (range, 9.8–111.0 mm). There were 38 cysts localized in the head/neck of the pancreas, whereas 58 cysts were localized in the body/tail. Approximately 46 cysts were regularly shaped, whereas 50 were irregularly shaped. The cystic fluid was viscous in 35 patients and thin in 61 patients. The median operation time was 23 minutes (range, 10–61 minutes). A 19-gauge needle was used in 76 patients, and a 22-gauge needle was used in 20 patients. Septation was recorded in most of the patients ($n = 57$), and the remaining 39 cysts were monocystic lesions. The pathological diagnosis was 1 true cyst, 1 bronchogenic cyst of the pancreas, 2 pseudocysts, 36 SCNs, 29 MCNs, 13 IPMNs, 7 SPNs, 2 NENs, and 5 cystadenocarcinomas. The basic characteristics of the patients are shown in Table 1.

Table 1

Basic characteristics of the 96 enrolled patients

Characteristics	Results
Age, mean (SD), y	47.6 (14.4)
Sex, *n* (%)	
Female	71 (74.0)
Male	25 (26.0)
Size, median (range), mm	43.4 (9.8–111.0)
Location, *n* (%)	
Head/neck	38 (39.6)
Body/tail	58 (60.4)
Shape, *n* (%)	
Regular	46 (47.9)
Irregular	50 (52.1)
Viscosity, *n* (%)	
Viscous	35 (36.5)
Thin	61 (63.5)
Operation time, median (range), min	23 (10–61)
Needle type, *n* (%)	
19-Gauge	76 (79.2)
22-Gauge	20 (20.8)
Pathological diagnosis, *n* (%)	
True cyst	1 (1.0)
Bronchogenic cyst of the pancreas	1 (1.1)
Pseudocysts	2 (2.1)
SCN	36 (37.5)
MCN	29 (30.2)
IPMN	13 (13.5)
SPN	7 (7.3)
NEN	2 (2.1)
Cystadenocarcinoma	5 (5.2)

IPMN, intraductal papillary neoplasm; MCN, mucinous cystic neoplasm; NEN, neuroendocrine neoplasm; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm.

Diagnostic value of the differentiation of benign and malignant PCNs

There were 7 malignant cysts, including 2 NENs and 5 cystadenocarcinomas. The remaining 89 cysts were classified as benign cysts. Liquid-based cytology analysis wrongly regarded 3 malignant cysts as benign cysts, whereas no benign cysts were misdiagnosed. Therefore, the overall diagnostic accuracy in the differentiation of benign and malignant PCNs was 96.9% (93/96). The sensitivity, specificity, positive predictive value, and negative predictive value of LBC were 57.1% (4/7), 100% (89/89), 100% (4/4), and 96.7% (89/92), respectively.

Diagnostic value of subtypes of PCNs

Among the 96 cysts enrolled, 43 cysts were given definitive diagnoses, whereas 53 were reported as cysts, PCNs, benign lesions, or no malignant signs without definitive diagnoses. Among the 43 cysts with definitive diagnoses, 32 were correctly classified, leading to a diagnostic accuracy of 74.4%. Six IPMNs were wrongly diagnosed as MCNs, 4 SCNs were wrongly diagnosed as MCNs, and 1 mucinous adenocarcinoma was diagnosed as an MCN. While taking all 96 patients into consideration, the overall diagnostic accuracy of LBC for specific cyst types was 33.3% (32/96).

To evaluate the factors affecting the diagnostic accuracy of the PCN subtypes, the patients were divided into 2 groups according to whether a definite diagnosis was given. The characteristics were compared between the definite diagnosis group ($n = 32$) and indefinite diagnosis group ($n = 64$). The clinical characteristics of the patients in the 2 groups are detailed in Table 2. In terms of age, sex, tumor size, cystic fluid viscosity, operation time, needle type, and presence of septation, no differences were found between the 2 groups (all $P > 0.05$). However, cysts in the pancreatic body/tail or exhibiting irregular shapes were more likely to obtain a definite LBC diagnosis.

DISCUSSION

Fine-needle aspiration cytology under abdominal ultrasound or CT guidance has been reported for more than 30 years.[39,40] Conventional smear (CS) used to be the most common cytopathologic analysis method. Wiersema et al[41] used EUS-guided CS to

Table 2

Characteristics of patients in the DD and ID groups

Characteristics	DD (*n* = 32)	ID (*n* = 64)	*P*
Age, mean (SD), y	48.1 (14.0)	47.3 (17.4)	0.803
Sex, *n* (%)			0.100
Female	27	44	
Male	5	20	
Size, median (range), mm	47.7 (23.5–88.8)	39.5 (9.8–111)	0.270
Location, *n* (%)			0.039
Head/neck	8	30	
Body/tail	24	34	
Shape, *n* (%)			0.021
Regular	10	36	
Irregular	22	28	
Viscosity, *n* (%)			0.881
Viscous	20	41	
Thin	12	23	
Operation time, median (range), min	24.5 (10–48)	22 (11–61)	0.264
Needle type, *n* (%)			0.155
19-Gauge	28	48	
22-Gauge	4	16	
Septation, *n* (%)			0.695
Yes	20	37	
No	12	27	

DD, definite diagnosis; ID, indefinite diagnosis.

evaluate the pathology of lymph nodes. Conventional smear was compared with EUS morphology in the evaluation of cystic pancreatic lesions, and the results showed that cytopathologic analysis did not enhance diagnostic yield and that EUS alone was sufficiently sensitive and accurate in identifying malignant PCLs.[42] The diagnostic value of CS was regarded to be decreased because of bloody smears, crushing artifacts, dry artifacts, and thick tissue fragments.[37,43] Liquid-based cytology was commonly used in the diagnosis of gynecological and thyroid diseases, but its application in pancreatic lesions was relatively rare, especially in PCNs.[44] Liquid-based cytology was able to achieve immediate fixation and storage of collected samples. In recent years, LBC, which allowed for optimal cell preservation, was introduced in the diagnosis of PCNs to overcome the crowding of cells and blood contamination of the CS in the analysis of pancreatic cystic fluid.[44–47]

Our study revealed that LBC successfully differentiated benign from malignant lesions in 96.9% of patients, and the diagnostic specificity of LBC was as high as 100%. The diagnostic values in our study were similar to those in the study by Chun et al,[37] which revealed that the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of LBC were 88.0%, 87.7%, 100%, 100%, and 16.7% for solid pancreatic neoplasms, respectively. It was possible that LBC might fail to detect malignant PCNs. However, if LBC displayed malignant signs, the lesion was malignant without a doubt. Unfortunately, LBC results can be disappointing because of the low cellularity obtained in the cystic fluid.[11,48] In our current study, the 3 malignant cysts that were misdiagnosed were all cystic-solid lesions. All 3 cysts were suspected to be malignant by EUS. However, we did not take the EUS modality into consideration. We suggest that LBC results alone are less convincing for cystic-solid lesions. The sensitivity revealed in our study failed to show the advantages of LBC over CS compared with that published in a meta-analysis.[8] This meta-analysis showed a sensitivity in differentiating mucinous cysts from nonmucinous cysts of 0.63 (95% CI, 0.56–0.70), whereas regarding adenocarcinoma that was malignant as benign mucinous cyst; however, the sensitivity evaluation in our study was to differentiate benign and malignant cysts. We speculated that the small size of malignant lesions also affected the evaluation of the sensitivity of LBC. When evaluating the diagnostic value of LBC in subtypes of PCNs, the overall diagnostic accuracy was 33.3%, much lower than the accuracy in distinguishing malignant from benign PCNs. We found that LBC failed to differentiate MCNs from IPMNs. Mucinous cystic neoplasms and IPMNs were classified as mucinous lesions with columnar epithelium in the cystic wall. The fluid was often viscous in these 2 kinds of cysts. Background mucin and neoplastic mucin-containing epithelium were demonstrated in the cytology of both MCN and IPMN. We could not differentiate these 2 kinds of mucinous cysts by LBC alone. However, EUS acted well in the differentiation between MCN and IPMN by evaluating whether the cyst communicated with the pancreatic duct. In this study, we defined all mucinous cysts revealed by LBC as MCN because of the inability of LBC to discriminate MCNs and IPMNs. If we did not distinguish between MCNs and IPMNs, the diagnostic value of LBC was believed to be higher. Rapid on-site evaluation plays an important role in the diagnosis of solid pancreatic lesions[49,50]; however, it has failed to be used in LBC for the diagnosis of PCNs.

We concluded that cysts located in the pancreatic body/tail or exhibiting an irregular shape predicted a definite LBC diagnosis. We suspected that the reasons for this result might be as follows. On the one hand, transgastric puncture was expected to be used to perform EUS-FNA when treating PCNs located in the pancreatic body and tail, whereas the transduodenal puncture was the better choice for PCNs located in the pancreatic head and neck. There was no doubt that transgastric puncture was easier than transduodenal puncture for cysts located in the pancreatic head and neck when using a 19-gauge needle. Puncture from the junction of the duodenal bulb and descending segment was especially challenging because it was not a stable position. On the other hand, cysts with irregular shapes were thought to have relatively larger surface areas. A larger surface area successfully provided more cells detached from the cyst wall for cystic fluid, ensuring the positive results of LBC. We suspected that the fluid volume should be regarded as an essential factor affecting the results of LBC. However, we recorded only the total volume of cystic fluid aspirated by EUS-FNA. In this retrospective study, we failed to calculate the exact volume of cystic fluid sent for LBC.

Although this was the first study to evaluate factors predicting positive LBC results in a relatively large sample, there were still several limitations. First, this was a single-center retrospective study. Some information was lost, for example, the cystic fluid volume sent for LBC. Second, the patients enrolled in our study were highly selected. Most (n = 207) of the 331 patients received LBC examinations. However, we excluded patients who did not undergo surgical resection without pathological results. Fewer than half of the patients who underwent LBC were analyzed. Patients enrolled in EUS-LA might have different characteristics from patients enrolled in surgical resection.[38,51,52] Cysts with communication between the cyst and pancreatic duct were not regarded as the indications for EUS-LA and were suggested for surgical resection or imaging surveillance. Malignant cysts were also excluded from EUS-LA. The mean size of the cysts enrolled in EUS-LA seems smaller than the cysts resected by surgical treatments in this study.[38] However, pathological results should be regarded as the criterion standard

when evaluating the diagnostic value of LBC. The study design made this bias inevitable. Third, evidence regarding the diagnostic value of LBC compared with other cytopathologic analysis methods, such as CS, was lacking. Finally, we failed to evaluate the safety of LBC by calculating the complications of LBC because LBC was performed under EUS-FNA, which also provides cystic fluid for biochemical and tumor marker analysis. We could evaluate only the complications of EUS-FNA, instead of LBC. Fortunately, no pancreatitis was noted after EUS-FNA. Multicenter, prospective, randomized controlled studies are warranted to confirm the value of LBC.

In conclusion, LBC is useful for differentiating benign PCNs from malignant PCNs with diagnostic accuracy as high as 96.9%. Liquid-based cytology alone can successfully characterize the PCN subtypes in one-third of patients, and PCNs located in the pancreatic body/tail or exhibiting irregular shapes are more likely to obtain a definite LBC diagnosis. EUS modality should be combined with LBC results to provide a final diagnosis in distinguishing between MCNs and IPMNs, whereas LBC fails to discriminate between these 2 subtypes of mucinous cysts.

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Ethical Approval

This study was approved by the institutional review board of Chinese PLA GeneralHospital and registered in the Chinese Clinical Trials Registry (no. ChiCTR-OOC-15006118)

Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collectionand analysis were performed by Chen Du, Zhengting He, Fei Gao and Xiuxue Feng. The first draft of the manuscript was written by Chen Du and Zhengting He and all authors commented on previous versions of the manuscript. All authors read and approved the previous versions of the manuscript. All authors read and approved the final manuscript. Chen Du and Zhengting He contributed equally to this study and should be regarded as co-first authors. Ningli Chai and Enqiang Linghu contributed equally to this study and should be regarded as co-corresponding authors.

References

1. Kimura W, Nagai H, Kuroda A, et al. Analysis of small cystic lesions of the pancreas. *Int J Pancreatol* 1995;18:197–206.
2. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015;148:819–22; quiz 812–813.
3. Bian Y, Jiang H, Zheng J, et al. Basic Pancreatic Lesions: Radiologic-pathologic Correlation. *J Transl Int Med* 2022;10:18–27.
4. Teoh AY, Seo DW, Brugge W, et al. Position statement on EUS-guided ablation of pancreatic cystic neoplasms from an international expert panel. *Endosc Int Open* 2019;7:E1064–E1077.
5. Garg R, Mohammed A, Singh A, et al. EUS-guided radiofrequency and ethanol ablation for pancreatic neuroendocrine tumors: a systematic review and meta-analysis. *Endosc Ultrasound* 2022;11:170–185.
6. Krishna S, Ardeshna D, Woods E, et al. An update on EUS-guided ablative techniques for pancreatic cystic lesions. *Endosc Ultrasound* 2022;11:432–441.
7. Aziz H, Acher AW, Krishna SG, et al. Comparison of society guidelines for the management and surveillance of pancreatic cysts: a review. *JAMA Surg* 2022;157:723–730.
8. Thosani N, Thosani S, Qiao W, et al. Role of EUS-FNA–based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. *Dig Dis Sci* 2010;55:2756–2766.
9. Elta GH, Enestvedt BK, Sauer BG, et al. ACG clinical guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol* 2018; 113:464–479.
10. Du C, Chai NL, Linghu EQ, et al. Comparison of endoscopic ultrasound, computed tomography and magnetic resonance imaging in assessment of detailed structures of pancreatic cystic neoplasms. *World J Gastroenterol* 2017;23:3184–3192.
11. Oguz D, Oztas E, Kalkan IH, et al. Accuracy of endoscopic ultrasound–guided fine needle aspiration cytology on the differentiation of malignant and benign pancreatic cystic lesions: a single-center experience. *J Dig Dis* 2013;14:132–139.
12. Larino-Noia J, de la Iglesia D, Iglesias-Garcia J, et al. 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;110:478–484.
13. Zhan XB, Wang B, Liu F, et al. Cyst fluid carcinoembryonic antigen concentration and cytology by endosonography-guided fine needle aspiration in predicting malignant pancreatic mucinous cystic neoplasms. *J Dig Dis* 2013;14:191–195.
14. 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.
15. Samarasena JB, Nakai Y, Chang KJ. Endoscopic ultrasonography-guided fine-needle aspiration of pancreatic cystic lesions: a practical approach to diagnosis and management. *Gastrointest Endosc Clin N Am* 2012;22: 169–185, vii.
16. Alkaade S, Chahla E, Levy M. Role of endoscopic ultrasound–guided fine-needle aspiration cytology, viscosity, and carcinoembryonic antigen in pancreatic cyst fluid. *Endosc Ultrasound* 2015;4:299–303.
17. Arguello L, Sanchez-Montes C, Mansilla-Vivar R, et al. Diagnostic yield of endoscopic ultrasound with fine-needle aspiration in pancreatic cystic lesions. *Gastroenterol Hepatol* 2020;43:1–8.
18. Sun L, Huang H, Jin Z. Application of EUS-based techniques in the evaluation of pancreatic cystic neoplasms. *Endosc Ultrasound.* 2021;10:230–240.
19. Oh SH, Lee JK, Lee KT, et al. The combination of cyst fluid carcinoembryonic antigen, cytology and viscosity increases the diagnostic accuracy of mucinous pancreatic cysts. *Gut Liver* 2017;11:283–289.
20. McCarty TR, Garg R, Rustagi T. Pancreatic cyst fluid glucose in differentiating mucinous from nonmucinous pancreatic cysts: a systematic review and meta-analysis. *Gastrointest Endosc* 2021;94:698–712.e6.
21. Guzman-Calderon E, Md BM, Casellas JA, et al. Intracystic glucose levels appear useful for diagnosis of pancreatic cystic lesions: a systematic review and meta-analysis. *Dig Dis Sci* 2022;67:2562–2570.
22. Rift CV, Scheie D, Toxvaerd A, et al. Diagnostic accuracy of EUS-guided through-the-needle-biopsies and simultaneously obtained fine needle aspiration for cytology from pancreatic cysts: a systematic review and meta-analysis. *Pathol Res Pract* 2021;220:153368.
23. Kovacevic B, Klausen P, Rift CV, et al. Clinical impact of endoscopic ultrasound–guided through-the-needle microbiopsy in patients with pancreatic cysts. *Endoscopy* 2021;53:44–52.
24. Krishna SG, Modi RM, Kamboj AK, et al. In vivo and ex vivo confocal endomicroscopy of pancreatic cystic lesions: a prospective study. *World J Gastroenterol* 2017;23:3338–3348.
25. Kovacevic B, Antonelli G, Klausen P, et al. EUS-guided biopsy versus confocal laser endomicroscopy in patients with pancreatic cystic lesions: a systematic review and meta-analysis. *Endosc Ultrasound* 2021;10:270–279.
26. Feng L, Guo J, Wang S, et al. Endoscopic Transmural Drainage and Necrosectomy in Acute Necrotizing Pancreatitis: A Review. *J Transl Int Med* 2021;9:168–176.

27. Napoleon B, Palazzo M, Lemaistre AI, et al. Needle-based confocal laser endomicroscopy of pancreatic cystic lesions: a prospective multicenter validation study in patients with definite diagnosis. *Endoscopy* 2019;51: 825–835.
28. Cheesman AR, Zhu H, Liao X, et al. Impact of EUS-guided microforceps biopsy sampling and needle-based confocal laser endomicroscopy on the diagnostic yield and clinical management of pancreatic cystic lesions. *Gastrointest Endosc* 2020;91:1095–1104.
29. Maker AV, Lee LS, Raut CP, et al. Cytology from pancreatic cysts has marginal utility in surgical decision-making. *Ann Surg Oncol* 2008;15: 3187–3192.
30. Ohno E, Hirooka Y, Kawashima H, et al. Endoscopic ultrasonography for the evaluation of pancreatic cystic neoplasms. *J Med Ultrason (2001)* 2020; 47:401–411.
31. Kamata K, Kitano M. Endoscopic diagnosis of cystic lesions of the pancreas. *Dig Endosc* 2019;31:5–15.
32. Okasha H, E Behiry M, Ramadan N, et al. Endoscopic ultrasound–guided fine needle aspiration in diagnosis of cystic pancreatic lesions. *Arab J Gastroenterol* 2019;20;86–90.
33. Lee LS. Updates in diagnosis and management of pancreatic cysts. *World J Gastroenterol* 2021;27:5700–5714.
34. Al-Haddad M, Gill KR, Raimondo M, et al. Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study. *Endoscopy* 2010;42:127–132.
35. Zhou W, Gao L, Wang SM, et al. Comparison of smear cytology and liquid-based cytology in EUS-guided FNA of pancreatic lesions: experience from a large tertiary center. *Gastrointest Endosc* 2020;91:932–942.
36. Yeon MH, Jeong HS, Lee HS, et al. Comparison of liquid-based cytology (CellPrepPlus) and conventional smears in pancreaticobiliary disease. *Korean J Intern Med* 2018;33:883–892.
37. Chun JW, Lee K, Lee SH, et al. Comparison of liquid-based cytology with conventional smear cytology for EUS-guided FNA of solid pancreatic masses: a prospective randomized noninferiority study. *Gastrointest Endosc* 2020;91:837–846.e831.
38. Du C, Chai N, Linghu E, et al. Long-term outcomes of EUS-guided lauromacrogol ablation for the treatment of pancreatic cystic neoplasms: 5 years of experience. *Endosc Ultrasound* 2022;11:44–52.
39. Jones EC, Suen KC, Grant DR, et al. Fine-needle aspiration cytology of neoplastic cysts of the pancreas. *Diagn Cytopathol* 1987;3:238–243.
40. Gupta RK, Scally J, Stewart RJ. Mucinous cystadenocarcinoma of the pancreas: diagnosis by fine-needle aspiration cytology. *Diagn Cytopathol* 1989;5:408–411.
41. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087–1095.
42. Sedlack R, Affi A, Vazquez-Sequeiros E, et al. Utility of EUS in the evaluation of cystic pancreatic lesions. *Gastrointest Endosc* 2002;56:543–547.
43. Ramai D, Singh J, Kani T, et al. Wet- versus dry-suction techniques for EUS-FNA of solid lesions: A systematic review and meta-analysis. *Endosc Ultrasound* 2021;10:319–324.
44. Chandan S, Mohan BP, Khan SR, et al. Comparison of EUS-guided conventional smear and liquid-based cytology in pancreatic lesions: a systematic review and meta-analysis. *Endosc Int Open* 2020;8:E1611–E1622.
45. Zhang XH, Ma SY, Liu N, et al. Comparison of smear cytology with liquid-based cytology in pancreatic lesions: a systematic review and meta-analysis. *World J Clin Cases* 2021;9:3308–3319.
46. de Luna R, Eloubeidi MA, Sheffield MV, et al. Comparison of ThinPrep and conventional preparations in pancreatic fine-needle aspiration biopsy. *Diagn Cytopathol* 2004;30:71–76.
47. LeBlanc JK, Emerson RE, Dewitt J, et al. A prospective study comparing rapid assessment of smears and ThinPrep for endoscopic ultrasound–guided fine-needle aspirates. *Endoscopy* 2010;42:389–394.
48. 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.
49. Facciorusso A, Gkolfakis P, Tziatzios G, et al. Comparison between EUS-guided fine-needle biopsy with or without rapid on-site evaluation for tissue sampling of solid pancreatic lesions: a systematic review and meta-analysis. *Endosc Ultrasound* 2022;11:458–465.
50. Nebel JA, Soldan M, Dumonceau JM, et al. Rapid on-site evaluation by endosonographer of endoscopic ultrasound fine-needle aspiration of solid pancreatic lesions: a randomized controlled trial. *Pancreas* 2021;50:815–821.
51. Linghu E, Du C, Chai N, et al. A prospective study on the safety and effectiveness of using lauromacrogol for ablation of pancreatic cystic neoplasms with the aid of EUS. *Gastrointest Endosc* 2017;86:872–880.
52. Du C, Chai NL, Linghu EQ, et al. Endoscopic ultrasound–guided injective ablative treatment of pancreatic cystic neoplasms. *World J Gastroenterol* 2020;26:3213–3224.