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EDITORIAL

Endoscopic techniques for the diagnosis of pancreatic cystic lesions

Sahib Singh, Saurabh Chandan, Rakesh Vinayek, Jahnvi Dhar, Jayanta Samanta, Gabriele Capurso, Ivo Boskoski, Cristiano Spada, Jorge D Machicado, Stefano Francesco Crinò, Antonio Facciorusso

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Sahib Singh, Department of Internal Medicine, Sinai Hospital, Baltimore, MD 21215, United States

Saurabh Chandan, Division of Gastroenterology and Hepatology, Creighton University School of Medicine, Omaha, NE 68131, United States

Rakesh Vinayek, Department of Gastroenterology, Sinai Hospital of Baltimore, Baltimore, MD 21215, United States

Jahnvi Dhar, Jayanta Samanta, Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Gabriele Capurso, Division of Pancreato-Biliary Endoscopy and Endosonography, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milano 20132, Italy

Ivo Boskoski, Digestive Endoscopy Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Università Cattolica del Sacro Cuore di Roma, Center for Endoscopic Research Therapeutics and Training, Roma 00168, Italy

Cristiano Spada, Department of Gastroenterology and Endoscopy, Catholic University, Roma 00168, Italy

Jorge D Machicado, Department of Gastroenterology, University of Michigan Health, Ann Arbor, MI 48107, United States

Stefano Francesco Crinò, Department of Endoscopy, University of Verona, Verona 37121, Veneto, Italy

Antonio Facciorusso, Gastroenterology Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia 71122, Italy

Corresponding author: Antonio Facciorusso, MD, PhD, Associate Professor, Gastroenterology Unit, Department of Medical and Surgical Sciences, University of Foggia, Via L Pinto 1 Foggia, Foggia 71122, Italy. antonio.facciorusso@virgilio.it

Abstract

Pancreatic cysts are mostly incidental findings on computed tomography or magnetic resonance imaging scans, with few patients presenting with abdominal pain or other symptoms. The accurate diagnosis of cysts is important as management depends on the type (neoplastic or non-neoplastic). Cross-sectional imaging is fast being replaced with endoscopic ultrasound (EUS) and various techniques based on that such as EUS-guided fine needle aspiration, EUS-guided needle confocal laser endomicroscopy, EUS-through-the-needle biopsy, and contrast-enhanced EUS. Clinical studies have reported varying diagnostic and adverse event rates with these modalities. In addition, American, European, and Kyoto guidelines for the diagnosis and management of pancreatic cysts have provided different recommendations. In this editorial, we elaborate on the clinical guidelines, recent studies, and comparison of different endoscopic methods for the diagnosis of pancreatic cysts.

Key Words: Endoscopic ultrasound; Fine needle aspiration; Needle confocal laser endomicroscopy; Through-the-needle biopsy; Contrast-enhanced endoscopic ultrasound

Core Tip: Endoscopic ultrasound has been the core diagnostic modality for patients found to have pancreatic cystic lesions on imaging, with subsequent differentiation based on techniques such as cystic fluid analysis (metabolites, molecular markers, and cytology), confocal laser endomicroscopy (to study the cyst epithelium), and microforceps biopsy. A combination of modalities, such as fluid analysis with microvasculature imaging, can further improve the diagnostic performance.

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INTRODUCTION

Pancreatic cysts are a common entity, with an incidence rate of about 2%-20% in patients undergoing computed tomography (CT) or magnetic resonance imaging (MRI) scans[1]. Most patients are asymptomatic, *i.e.* cysts are found incidentally, with only few presenting with complaints such as abdominal pain and weight loss. A history of pancreatitis or family history of pancreatic cancer confers an additional risk of developing pancreatic cysts. These can be neoplastic such as mucinous cystic neoplasms, intraductal papillary mucinous neoplasms (IPMNs), cystic neuroendocrine tumors, and solid pseudopapillary neoplasms; or non-neoplastic such as simple cysts, serous cystic adenomas, mucinous non-neoplastic cysts, and lymphoepithelial cysts[2]. Management of pancreatic cysts is dependent on the type; hence accurate diagnosis is of paramount importance[3].

The usual approach after finding pancreatic cysts on CT/MRI is analysis of the cyst fluid obtained *via* endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA)[4-8]. Common tests include levels of carcinoembryonic antigen (CEA), amylase and glucose, and cytology. Upcoming technologies such as next-generation sequencing (NGS) for the molecular analysis of cyst fluid allow for better neoplastic assessment[9]. Further, modifications of EUS including EUS-guided needle confocal laser endomicroscopy (nCLE), EUS-through-the-needle biopsy (TTNB), and contrast-enhanced EUS (CE-EUS) have been introduced, which greatly enhance the diagnostic capability of EUS[10-13]. Several clinical studies have shown excellent performance of these newer modalities for pancreatic cysts[14].

In this editorial, we discuss the currently available guidelines and the recent studies evaluating various endoscopic techniques for diagnosis of pancreatic cystic lesions.

GUIDELINES

The 2015 American Gastroenterological Association guidelines suggested: (1) EUS-FNA for examination of pancreatic cysts with ≥ 2 high-risk features (dilated main pancreatic duct, size ≥ 3 cm, presence of a solid component); (2) MRI surveillance in patients with benign results on EUS-FNA; (3) Repeat EUS-FNA in patients developing any of the high-risk features during surveillance; and (4) Surgery in patients with combination of dilated pancreatic duct, solid component and/or high-risk features on EUS-FNA[15].

Expanding the criteria further, the American College of Gastroenterology (ACG) 2018 advised: (1) MRI as the diagnostic test of choice for characterizing pancreatic cysts, with EUS or pancreatic CT as alternatives; (2) EUS-FNA with fluid analysis (CEA, cytology, molecular markers) in patients with indeterminate cysts; (3) EUS ± FNA in patients with mucinous cystic neoplasms or IPMNs who are either symptomatic (diabetes, pancreatitis, jaundice), have concerning features on imaging (> 3 mm increase in size per year, solid component), or dysplastic features on cytology; and (4) EUS for surveillance in patients unable to undergo MRI[16].

In comparison to ACG/American Gastroenterological Association, the 2018 European guidelines presented a separate section dedicated to endoscopy: (1) EUS as an alternative to imaging modalities, with special consideration in patients with concerning radiological or clinical features; (2) Contrast harmonic-enhanced EUS (CH-EUS) for characterization of mural nodules, septations and cyst vascularity, followed by EUS-FNA of the concerning areas; (3) EUS-FNA, with cyst fluid analysis, to differentiate mucinous/non-mucinous and benign/malignant cysts, but only in patients in whom diagnosis was not clear on imaging or no clear surgical indication is present; (4) Endoscopic retrograde cholangiopancreatography and EUS-nCLE not to be used for characterizing pancreatic cysts due to risk of adverse events (AEs); and (5) Pancreatoscopy only in select cases of main duct-IPMNs[17]. Recently, Ohtsuka *et al*[18] released the 2024 Kyoto guidelines for IPMN management. EUS-FNA and CE-EUS were recommended for suspected high-grade dysplasia/invasive carcinoma in patients with IPMNs (evidence level 2++, grade C). Endoscopic retrograde cholangiopancreatography was advised only for biliary drainage in patients with IPMNs with jaundice.

The varying recommendations from different societies have created confusion among the providers, with no clear consensus on the appropriate path to follow. Aziz *et al*[19] advised that the currently available guidelines are based on low-quality evidence without adequate updates, and provide differing advice for surveillance, treatment, and follow-up, necessitating referral to tertiary care centers with multidisciplinary teams. In observational studies of patients with IPMNs who underwent surgery, Perez *et al*[20] and van Huijgevoort *et al*[21] reported that ACG and European guidelines have the highest sensitivity in identifying IPMN cases with high-grade dysplasia/malignancy, but this also resulted in more surgical procedures for those without advanced neoplastic features. Evaluating the quality of the guidelines, John *et al*[22] gave a rate of 69% presentation clarity and 14% applicability. Even with the multitude of guidelines available, patient care would likely not improve until these are properly followed. Zouridis *et al*[23] conducted a retrospective study of patients with pancreatic cysts, and found that only 33% patients had appropriate follow-up, of whom 31% had IPMNs and 43% had pseudocysts.

ENDOSCOPIC DIAGNOSTIC MODALITIES

EUS

Imaging of the pancreatic cysts by EUS alone has shown variable characterization rates compared with CT/MRI[3,24]. In a recent study by Hesse *et al*[7], follow-up EUS and MRI in patients with IPMNs showed a mean difference of 0.55 mm (maximal diameter), which could significantly alter subsequent management. Schedel *et al*[25] reported that EUS was able to diagnose pancreatic cysts in 223 of 455 patients - branch duct IPMNs (61.9%), main duct IPMNs (7.2%), and mixed-type IPMNs (2.2%).

EUS-FNA

Sampling and analysis of the pancreatic cyst *via* FNA are currently the main roles of EUS in these patients[26,27]. As the position of EUS-FNA is already established in clinical guidelines, recent studies have primarily focused on demonstrating the diagnostic ability of different markers obtained from pancreatic cyst FNA. Ribeiro *et al*[28] reported that on-site measurement of intracystic glucose has better sensitivity of identifying mucinous cysts (93.2%) compared to CEA (55.6%), along with a high correlation with glucose measured in the laboratory (P = 0.919). A similar finding was reported by Rossi *et al*[29], who also showed that intracystic lactate levels correspond with the glucose trends. Combining the various cystic fluid biomarkers, such as glucose, CEA, amylase, and vascular endothelial growth factor, Yip-Schneider *et al*[30] found a diagnostic rate of 93% (surgical cohort) and 100% (surveillance cohort) for serous pancreatic cysts.

In an observational study of 96 patients conducted by Du *et al*[31], EUS-FNA-based fluid cytology showed a high performance in differentiating benign and malignant cysts (96.9% diagnostic accuracy, 57.1% sensitivity, 100% specificity, 100% positive predictive value [PPV] and 96.7% negative predictive value [NPV]), but only a 33.3% accuracy rate for identifying specific types of cysts. Further, pancreatic body/tail cysts and those with irregular shape had a higher likelihood of being correctly diagnosed by cytology. Seyfedinova *et al*[32] evaluated the efficacy of EUS-FNA for RNA profiling of pancreatic cysts, with 70% of the cyst fluid samples having successful RNA extraction. Fluids from mucinous cysts were found to have higher RNA profiling quality (*i.e.* purity, concentration, and integrity) than serous cyst samples [33]. Going a step forward, Paniccia *et al*[34] conducted a large multicenter (31 institutions) prospective study, in which NGS (22 gene panel) of cystic fluid obtained *via* EUS-FNA demonstrated a high sensitivity and specificity for identifying various types of pancreatic cysts, mucinous cyst neoplasias, and the propensity of interval growth and distant metastasis.

Combining the EUS-FNA fluid analysis with microvasculature imaging, Carrara *et al*[35] reported improvement in diagnosis of pancreatic cysts compared with fluid analysis alone - sensitivity (97.3% *vs* 76.7%), specificity (77.1% *vs* 56.7%), PPV (90.1% *vs* 77.8%), NPV (93.1% *vs* 55.3%), and accuracy (73.2% *vs* 56%). Shedding light on the pancreatitis risk post EUS-FNA, Magahis *et al*[36] performed a meta-analysis of 64 studies (8086 patients), which revealed only a 1.4% pooled risk of pancreatitis – the majority were mild in severity (67%) with no associated mortality.

EUS-nCLE

Given the accuracy rate of about 65%-75% of EUS ± FNA in diagnosing IPMN neoplasias, a new diagnostic modality (EUS-nCLE) was developed[37]. In this technique, the pancreatic cyst epithelium is examined *via* a nCLE probe during the EUS procedure. This allows for the video sequence to be reviewed later for characterizing atypia, along with simultaneous fluid analysis obtained during EUS. Clinical studies reported about 70%-90% accuracy rate using EUS-nCLE[38].

A limitation to the use of EUS-nCLE is the learning curve required to attain efficacy by the endoscopists. Machicado *et al* [39] conducted a prospective study to evaluate the impact of nCLE teaching videos on early career endo-sonographers. After the structured training program, the participants achieved an accuracy rate of 82%-96% in differentiating pancreatic cyst types, along with improved confidence and significant agreement between the observers. To further enhance the capability of EUS-nCLE, artificial intelligence techniques such as convolutional neural network based models have been trained and tested on the EUS-nCLE images which greatly improve the diagnostic accuracy compared with manual interpretation[37,40,41].

EUS-TTNB

The greater amount of specimen obtained through EUS-guided TTNB of the pancreatic cysts, using microforceps (diameter around 0.8 mm), meant better diagnostics were possible as compared to EUS-FNA samples[42]. This is due to the possibility to retrieve a sample containing epithelium and stroma, and suitable for several immune-histochemical analyses[43]. However, this also resulted in increased risk of AEs, leading to less than desired adoption among the proceduralists. In the prospective study of 40 patients by Vilas-Boas *et al*[44], the technical success of EUS-TTNB was reported to be 97.5%, with higher diagnostic yield when compared with FNA cytology/fluid analysis (72.5% *vs* 27.5%). Additionally, the sensitivity of TTNB was also higher than cytology (76% *vs* 35%), and subtyping could be done in 63% of patients with IPMN. Only 3 AEs were reported, with 2 cases of bleeding (self-limited) and 1 abdominal pain.

Ahmed *et al*[45] performed a retrospective study of EUS-TTNB (34 patients) and found 100% technical success rate, with adequate histological samples being obtained in 74% cases. Around 71% patients had change in management after EUS-TTNB. Post EUS pancreatitis was reported in 2 patients and another 1 had intracystic bleeding. Integrating NGS with EUS-TTNB, Rift *et al*[46] demonstrated a high sensitivity and specificity for diagnosis of mucinous cyst (83.7% and 81.8%) and IPMN (87.2% and 84.6%) respectively. The efficacy of EUS-TTNB beyond usual pancreatic cysts was reported in the study by Conti Bellocchi *et al*[47], in which successful diagnosis was made in 24 of 26 patients with uncommon cystic lesions such as squamoid cysts, lymphoepithelial cysts and cystic neuroendocrine tumors.

Pooling the available evidence for EUS-TTNB, Gopakumar and Puli[48] conducted a meta-analysis of 11 studies (575 patients), with mean age 62.25 years and 61.39% females. For classifying pancreatic cysts as neoplastic/non-neoplastic, EUS-TTNB showed sensitivity of 76.60% and specificity of 98.90%, with the odds ratio for diagnosis being 41.34. Around 3.04% patients developed pancreatitis and 4.02% had intracystic bleeding. Importantly, a good interobserver agreement among pathologists was demonstrated for the evaluation of EUS-TTNB samples[49]. The recursive partitioning analysis of a large multicenter series enrolling 506 patients identified three risk classes for AEs: High-risk (IPMN sampled with multiple microforceps passes, 28% AEs rate), low-risk (1.4% AEs rate, including patients < 64 years with other-than-IPMN diagnosis sampled with ≤ 2 microforceps passes and with complete aspiration of the cyst), and middle-risk class (6.1% AEs rate, including the remaining patients)[50]. Therefore, the authors concluded that EUS-TTNB should be avoided in cysts in communication with main pancreatic duct, particularly if subject to multiple microforceps passes. The results of these studies emphasize the importance of the accurate patient selection for this procedure.

CH-EUS

CE-EUS was initially developed to improve lesion characterization during EUS by the simultaneous injection of intravenous contrast, but it was limited in analysis of microvessels and was confounded by the presence of artifacts[51]. Subsequently, modification was made to the EUS component by introduction of a wideband transducer and a new processor that could produce harmonic imaging (CH-EUS)[52]. This enabled microbubble detection with reduced artifacts. Although it enhances the quality of data obtained, CH-EUS is costly and has a steep learning curve. A recent meta-analysis showed a pooled sensitivity of CE-EUS of 88.2% (82.7%-92.5%), increased to 97.0% (95% confidence interval: 92.5%-99.2%) with CH-EUS[53].

EUS-guided sulfur hexafluoride pancreatography

Newer experimental iterations of EUS have been coming up recently, such as sulfur hexafluoride injection into the pancreatic cyst during EUS for evaluation of any communication between the pancreatic duct and the cyst, as reported by Li *et al*[54]. This EUS-guided sulfur hexafluoride pancreatography was able to determine the duct-cyst connection with a high accuracy (96.6%), sensitivity (88.9%), specificity (100%), PPV (100%), and NPV (95.2%).

CLINICAL IMPLICATIONS

As the different EUS-based diagnostic modalities for pancreatic cysts have shown varying efficacies, it becomes difficult to choose the most appropriate one in clinical practice by the gastroenterologists. Li *et al*[55] published a network meta-analysis of 40 studies (3641 patients) comparing the EUS-based techniques. For differentiating mucinous cysts, EUS-nCLE and EUS-TTNB had the highest superiority indices (12.25 [2.33-19.00] and 11.60 [1.00-19.00], respectively). The latter also showed greatest superiority for malignant cysts compared to other methods (13.93 [5.00-15.00]). Among the specific markers for mucinous cysts diagnosis, glucose had high sensitivity and molecular mutations had high specificity.

CONCLUSION

Endoscopy, in particular EUS, has become one of the cornerstone diagnostic modalities for identification and differentiation of pancreatic cysts. It is a rapidly evolving field, with numerous clinical studies and comparisons being published at a high rate. There is a clear need for update in the clinical guidelines to incorporate the findings of the new studies, as well as provide the clinicians with structured recommendations to pursue the evaluation of pancreatic cysts.

FOOTNOTES

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Country of origin: Italy

ORCID number: Sahib Singh 0000-0001-5660-782X; Saurabh Chandan 0000-0002-2661-6693; Jahnvi Dhar 0000-0002-6929-4276; Jayanta Samanta 0000-0002-9277-5086; Gabriele Capurso 0000-0002-0019-8753; Ivo Boskoski 0000-0001-8194-2670; Antonio Facciorusso 0000-0002-2107-2156.

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