Pancreatic cysts are a heterogenous group of lesions that can be differentiated into mucinous and non-mucinous cysts based on their malignant potential. Cross-sectional imaging alone is inadequate to reliably distinguish between the two groups. Endoscopic ultrasound (EUS) and fine needle aspiration has been used for analysis of the cyst morphology and cyst fluid. Traditional markers such as fluid carcinoembryonic antigen and cytology have been useful particularly for the assessment of indeterminate cysts or those with high-risk features, but the overall diagnostic accuracy is still sub-par. As a result, new techniques have been described to improve the ability of EUS to risk stratify a pancreatic cyst. In this review, we describe some of the novel EUS-based techniques in the evaluation of pancreatic cysts, namely needle-based confocal laser endomicroscopy, through the needle cystoscopy, and through the needle biopsy techniques.

Keywords: Pancreatic cyst; Endosonography; Microscopy, confocal; Cystoscopy; Biopsy, fine-needle

INTRODUCTION

When evaluating a pancreatic cyst, there are three main issues that will need to be addressed. Firstly, whether the cyst is malignant or benign. Secondly, if the cyst is benign, we need to know whether the cyst is mucinous or non-mucinous. The former has malignant potential, whilst the latter has no malignant potential. Lastly, if mucinous, we need to know what its malignant potential is within the patient’s lifetime. By knowing these characteristics, the physician will be able to decide on the appropriate management strategy for each pancreatic cyst: benign lesions will not require repetitive and costly surveillance; low-risk lesions can avoid unnecessary surgery, and high-risk lesions can undergo surveillance at the required intervals to try to identify cancer in its early stages.

Imaging modalities such as computed tomography or magnetic resonance imaging scans are not always able to reliably identify the exact type of pancreatic cysts. Endoscopic ultrasound (EUS) and fine needle aspiration (FNA) is often done as an adjunctive imaging modality. However, EUS-guided FNA has proven largely suboptimal in accurately diagnosing pancreatic cysts, with a reported diagnostic yield of only 47%. Analysis of additional cyst fluid markers such as fluid carcinoembryonic antigen has also been traditionally used to increase the accuracy of differentiating between mucinous and non-mucinous cysts. Nevertheless, the reported sensitivity of 61% and specificity of 77% is also unsatisfactory for the risk stratification of potentially malignant pancreatic cysts.
As a result, new invasive techniques have been developed to improve the ability of EUS to risk stratify a pancreatic cyst. In this review, we describe some of the novel EUS-based techniques in the evaluation of pancreatic cysts, namely needle-based confocal laser endomicroscopy, through the needle cystoscopy, and through the needle biopsy techniques.

MAIN BODY

1. EUS-based novel invasive modalities for the evaluation of pancreatic cysts

1) Needle-based confocal laser endomicroscopy (nCLE)

EUS-guided needle-based confocal laser endomicroscopy is a technique that allows direct visualization and microscopic evaluation of the surface epithelium of pancreatic cyst walls. To begin with, intravenous fluorescein is injected 2-3 minutes prior to the procedure. The cyst wall is then punctured with a 19G FNA needle, and a preloaded small-calibre confocal laser endomicroscopy (CLE) probe is subsequently advanced under EUS-guidance into the pancreatic cyst. By placing the probe in contact with the intracystic epithelium, cellular images of a high magnification and resolution can be obtained, facilitating real-time in vivo histopathological assessment of pancreatic cystic lesions.

The different vascular and epithelial patterns visualized can be used to differentiate between pancreatic cystic lesions, and characteristic features have been described with high specificity. Mucinous cystic lesions have epithelial bands, and a branched or rope-ladder vascular pattern. Intraductal papillary mucinous neoplasms (IPMNs) have papillary projections with a branched or rope-ladder vascular pattern. Pseudocysts have a dark background with bright particles, while serous cystadenomas have a classical ‘fern pattern’ of vascularity described as the superficial characteristic network. Cystic neuroendocrine tumours have been found to have a trabecular pattern. A recent meta-analysis has confirmed a high diagnostic accuracy of 83% for pancreatic lesions, with a sensitivity and specificity of 85% and 90% respectively. EUS-guided nCLE has also been consistently shown to have a superior diagnostic accuracy, sensitivity, and specificity compared to using either EUS alone or EUS-FNA.

Early studies raised some concerns about the safety of this procedure, but subsequent studies have shown that there is no increase in the rate of adverse events when compared against EUS-FNA. The most common adverse event is post-procedural pancreatitis with an incidence rate of 1.2-6.7%. Rarer adverse events include intracystic bleeding, cyst infection, and peri-pancreatic fluid collections. To minimize these risks, a consensus group has recommended that the EUS-guided nCLE procedure be kept as short as possible (ideally less than 6 minutes) with minimal catheter manipulation, and that the probe should be removed once sufficient diagnostic criterion is observed and the pancreatic cystic lesion can be classified.

Despite its diagnostic superiority, several factors have hampered its uptake amongst endosonographers, chief of which being the cost of implementation. Not only does the proprietary platform have a high upfront cost; the probes, while re-usable, also have a limited lifespan. Furthermore, this procedure has a steep learning curve. Ample training is needed for endosonographers to become proficient enough to double up as real-time histopathologists, and yet interobserver disagreement on image interpretation is still often seen. The use of artificial intelligence systems has shown some potential in resolving this issue, with a study showing that convolutional neural network algorithmic models were accurate in risk stratification of IPMNs. However, more research needs to be done to determine its role in the evaluation of pancreatic cysts.

2) Through-the-needle cystoscopy

The SpyGlass fiberoptic probe can be introduced through the 19G FNA needle into the cyst. This enables direct visualization of cyst content as well as inner cyst wall, which could help with identification of different pancreatic cystic lesions based on their imaging characteristics. Mucinous cysts have been described as having smooth cyst walls with cloudy fluid. IPMNs showed papilla-like protrusions and a mucin cloud, whereas serous cystadenomas are more likely to have smooth cyst walls with a tree-like branching pattern of blood vessels.

However, these findings have not been proven to be robust enough to make a diagnosis based solely on cystoscopy findings. In the prospective DETECT study, the only significant association in high-certainty patients was found between the presence of mucin
on cystoscopy and mucinous cysts (sensitivity 90%, p=0.0004). The other imaging characteristics of cyst wall blood vessels, presence of intracystic partitions, and papilla-like protrusions were not reliable.

Furthermore, even though clear images are critical for accurate image characterization, cystoscopy images tend to be vague and suboptimal. This is partly due to presence of thick or cloudy fluid within cysts, which can be seen in up to 45% of cysts. In addition, the focal length required for the fiberoptic probe is 4-7 mm, which can make it difficult to achieve the necessary distance particularly in smaller cysts. Limited tip angulation also makes full visualization of the cyst challenging.

While the use of cystoscopy is restricted by the aforementioned issues, it has shown more promise when used in conjunction with other evaluation methods, such as EUS-guided nCLE. The distribution of abnormal tissue within an individual pancreatic cyst can be heterogeneous and spotty. Using the cystoscope to first detect focal abnormalities can bring about the opportunity to guide the nCLE probe to the target region, increasing diagnostic yield. The DETECT study demonstrated this by showing a higher sensitivity and accuracy when combining cystoscopy and nCLE as compared to when either modality was used alone.

3) Through-the-needle microforceps biopsy (TTNB)

The microforceps, which has open serrated jaws, is designed to be advanced through a 19G FNA needle. It can obtain targeted tissue samples from the cyst wall, septa, or mural nodules under EUS guidance. This sampling method has been consistently demonstrated to have a high technical success rate, irrespective of the location of the cyst within the pancreas. TTNB is superior to EUS-FNA in its ability to attain histological core specimens, with a meta-analysis showing a histological adequacy rate of 87%. This allows for improved tissue architecture interpretation and the opportunity to reliably define cyst histotype preoperatively, which can prevent patients from undergoing unwarranted surveillance or surgery.

The diagnostic yield of TTNB has been estimated to be 69.5-72.5% from multiple studies—again, significantly better than with EUS-FNA sampling alone. It is able to differentiate between mucinous and non-mucinous cysts well, with a high sensitivity and specificity of 88.6-90.1% and 94.0-94.7% respectively for mucinous cysts. TTNB also showed a high level of concordance of 82.3-93.0% with post-operative surgical pathology, and was significantly more likely to match the diagnosis on surgical pathology when compared against cytology. In addition, several studies have shown that the histological grading of mucinous cysts on TTNB histology was of significantly higher concordance with surgical pathology versus FNA, allowing physicians to risk-stratify the pancreatic cysts even more accurately.

Unfortunately, TTNB is only able to provide information on focal pieces of the cyst, which may not be representative of the overall lesion given cyst wall heterogeneity. nCLE prior to TTNB has been proposed as a method for increasing diagnostic yield by guiding the microforceps to the most abnormal area. The results of one study combining nCLE with TTNB showed a significant improvement in obtaining a specific pancreatic cyst diagnosis when compared to standard evaluation. This also led to a change in diagnosis of the pancreatic cyst in at least 1/3rd of cases, which in turn resulted a major impact in clinical management.

Safety concerns have been a factor deterring many clinicians from utilizing TTNB. The overall complication rate can range up to 12.5%, including intracystic bleeding, pancreatitis, infection, and abdominal pain. While most are mild and self-limiting, there is a non-negligible rate of moderate to severe adverse events. One study showed that 25% of adverse events experienced were classified as moderate, 15% were classified as severe, and 5% of adverse events experienced were ultimately fatal. The number of microforceps passes, complete aspiration of the cyst, and diagnosis of IPMN were found to be significant predictors of adverse events. Careful selection of patients based on their age and co-morbidities is essential before deciding to perform the procedure.

CONCLUSION

EUS-FNA alone is suboptimal for the classification and risk stratification of pancreatic cysts. Novel EUS-based modalities to address this deficiency have shown promise—nCLE, TTNB, and cystoscopy. All of these in isolation have their strengths. However, these diagnostic investigations are more accurate when used in
tandem with each other. Several studies have already shown the superiority of combined techniques (EUS-guided nCLE and/or TTNB followed by FNA) in diagnostic accuracy of pancreatic cystic lesions. Future studies should continue to explore the best way to integrate these techniques together in a cohesive diagnostic algorithm.

Conflicts of Interest

The authors have no conflicts to disclose.

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REFERENCES

21. Crinò SF, Bernardoni L, Brozzi L, et al. Association between macroscopically visible tissue samples and diagnostic accuracy of EUS-guided...