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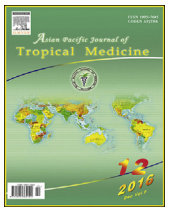

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EUS for pancreatic cystic neoplasms: The roadmap to the future is much more than just a few shades of gray

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ABSTRACT

Pancreatic cystic and neoplasms are being diagnosed with increasing frequency. Accurate diagnosis and determination of benign versus malignant lesions is crucial for determining need for surveillance versus surgery or endoscopic therapy as well as avoiding unnecessary surgery in cysts with no malignant potential. Tumor markers such as KRAS and GNAS hold promise, but which molecular marker or a combination of markers is most useful and cost effective remains to be seen. Advanced imaging with confocal laser endomicroscopy can serve as an optical biopsy and play a part in the diagnostic algorithm. Microforceps aided biopsy of pancreatic cyst wall and tumor contents hold great promise as they allow direct tissue acquisition. Much progress has been made in the role of EUS guided evaluation of pancreatic cystic neoplasms over the last several years, and with the advances enumerated above, the future is more than just a few shades of gray. Future studies should include prospective multi-arm trials of microforceps biopsy versus conventional EUS-FNA and use of biochemical and molecular markers, confocal laser endomicroscopy or a combination thereof to determine best approach to pancreatic cystic neoplasms. In Osler's words, 'Medicine is a science of uncertainty and an art of probability'. Incorporation of advanced imaging and molecular markers into a new diagnostic algorithm with subsequent validation through retrospective and prospective studies has the potential to increase diagnostic accuracy and guide optimal management of patients and improve outcomes.

1. Introduction

Ever since the advent of endoscopic ultrasound in the 1980s, the scope of EUS guided interventions has broadened in parallel to technical advances such as refinement in image quality and better understanding of the endosonographic anatomy.

Today, a repertoire of more than a dozen therapeutic interventions exist in the advanced endoscopist's armamentarium for diagnosis, staging and treatment of pancreato-biliary and other gastrointestinal malignancies as well as benign conditions.

EUS is routinely used today in clinical practice for staging of esophageal, gastric, colonic as well as pancreatic and biliary tumors. EUS-FNA and core biopsies form some of the standard diagnostic interventions aided by EUS. More recent advances in technology have the potential to take the diagnostic and therapeutic value of EUS to a higher level, allowing for more diagnostic accuracy and broader range of therapeutic interventions.

2. Role of EUS-FNA and new biochemical and molecular markers obtained by cyst fluid aspiration in diagnosis of pancreatic cystic neoplasms

EUS-FNA has already been established to be superior to multi-detector CT for diagnosis of pancreatic neoplasms less than 2 cm in size in patients with clinical symptoms suggestive of malignancy but a negative CT scan [1].

EUS not only helps in assessing size, extent and features concerning for malignancy such as ductal dilation, mural nodules and vascular invasion [2], but it also allows for sampling the cyst for on site cytology as well for obtaining markers such as CEA, which is presently the most commonly utilized biochemical marker across the United States [3]. Worthy of mentioning here is the

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Cooperative Pancreatic Study by Brugge *et al.*, which established that CEA was the only tumor marker useful for distinguishing mucinous cysts from non mucinous cysts, when the level was>192 ng/mL, although the sensitivity was only 73% [4].

Apart from EUS-FNA and core biopsies, a cytobrush is available to increase the cellular yield from pancreatic cystic lesions. Indeed, a prospective study involving tandem EUS-FNA and EUS guided cytobrushings showed that the yield of intracellular mucin was significantly more with cytobrushings [5]. Another study showed a statistically proven superiority of EUS guided cytology brushings over fluid aspiration [6], however the complication rate in this small study was unacceptably high with cytobrushings, limiting its use.

As an adjunct to cytology, there has been an interest in the diagnostic utility of biomarkers from cyst fluid [7]. A recent multicenter center using a panel of biomarkers showed that serous cystadenomas could be identified with a sensitivity of 100% and specificity of 91% by presence of the marker VHL and chromosome 3 LOH and by the absence of a KRAS, GNAS, RNF43 mutation or by the absence of aneuploidy in chromosome 5p or 8p [8].

IPMNs were identified with 76% sensitivity and 97% specificity by the presence of a mutation in GNAS, RNF43, LOH in chromosome 9, aneuploidy in chromosome 1q or 8p [8]. Solid pseudopapillary tumors were identified with 100% sensitivity and 100% specificity by the presence of a CTNNB1 mutation and the absence of KRAS, GNAS, or RNF43 mutations or chromosome 18 LOH [8]. Tumor markers could alleviate some of the diagnostic roadblocks encountered when cellularity from EUS-FNA is inadequate or the cytology read is indeterminate for dysplasia.

3. Safety of EUS guided sampling

EUS-FNA breaches the gut wall barrier and there is potential for adverse events such as bleeding, perforation, infection and concern for peritoneal seeding from malignant cystic neoplasms. EUS-FNA, however, has been established to be very safe, with overall adverse event rate ranging from 0% to 2.5% [9].

Even though EUS guided cytobrush sampling has proved to give much higher yields and provide an accurate diagnosis, we currently do not recommend it given the risk of unacceptably high complications of 10%, including one death due to delayed retroperitoneal hemorrhage in one patient to date [5].

There has been concern for peritoneal seeding from FNA in IPMNs which harbor malignancy, however the PIPE study showed no significant different in rate of peritoneal seeding when compared to patients who had surgery for pancreatic cystic lesions but who did not undergo preoperative EUS guided sampling [10].

4. Real time ‘optical diagnosis’ of pancreatic cystic neoplasms using needle based confocal laser endomicroscopy

Optical diagnosis of lesions with malignant potential remains the holy grail of advanced imaging techniques. Recent advancements have allowed a small needle based confocal endomicroscopy probe (nCLE) (AQ Flex 19, Mauna Kea technologies, Paris, France) to be passed through the 19 G EUS-FNA needle [11].

The INSPECT and DETECT trial require special mention here. The INSPECT trial, was a pilot study involving 8 centers using nCLE and it established descriptive terminologies for imaging findings on nCLE obtained from the pancreatic parenchyma, epithelial cyst structures and from the cyst lumen. Examples of descriptive terms include ‘finger like papillary projections’ and ‘dark aggregates of cells’. This study also established their histopathologic co-relates and demonstrated a 100% PPV in identifying IPMNs when ‘villous structures’ were seen on nCLE [12].

A subsequent study, called the DETECT trial utilized probe based pancreatic cystoscopy using direct visualization with Spyglass (Spyglass DS, Boston Scientific, USA) combined with nCLE and showed that the combination of mucin on Spyglass cystoscopy and papillary projections or dark rings on nCLE had a sensitivity of 93% and specificity of 88% for diagnosis of mucinous cysts in patient with high certainty diagnosis, which was defined as cases where surgical pathology was not available but two independent investigators agreed with a concordant diagnosis [13].

5. EUS guided chemical ablation of pancreatic cystic lesions

For patients with pancreatic cysts that merit surgical resection but who are poor surgical candidates, EUS guided chemical ablation remains a theoretically appealing alternative due to the morbidity associated with pancreatic surgery [14].

Ethanol alone and ethanol followed by paclitaxel have been commonly used agents with success rate ranging from 38% to 79%, defined as complete resolution of cystic lesions [15,16]. Complications of this technique range from mild abdominal pain to pancreatitis and even portal vein thrombosis [17].

Several prior studies assessing response of ethanol injection or lavage did not standardize the technique and ethanol concentration or volume of ethanol instilled into the cyst cavity.

A recent ten year prospective study by Topazian *et al.* showed that EUS guided ethanol lavage showed dismal results with respect to complete ablation of pancreatic cyst, as seen by complete resolution of cysts in only 9% of patients [18]. Thus, EUS guided chemoablation of pancreatic cystic neoplasms in carefully selected non-surgical candidates may be attempted, however the data is less than promising and search for better non-surgical ablative techniques is warranted.

6. EUS-guided RFA of pancreatic lesions

Radiofrequency ablation is well established for eradication of dysplastic Barrett's esophagus as well as hepatocellular carcinoma, however, the use of EUS-RFA for ablation of pancreatic cystic lesions is still in the realm of case reports and pilot studies and may become more popular if future studies show promising data.

A South Korean study of 6 patients with unresectable pancreatic cancer demonstrated that RFA of pancreatic tumors through an EUS guided approach was feasible, and aside from abdominal pain that could be controlled with analgesics, there were no adverse events such as pancreatitis, bleeding, duodenal injury, or portal vein or splenic vein thrombosis [19].

EUS guided RFA holds promise in ablation of discrete lesions such as neuroendocrine tumors of the pancreas in patients

who may be otherwise poor surgical candidates due to other comorbidities. Indeed, a recent study by Lakhtakia *et al.* showed successful RFA of symptomatic insulinomas smaller than 22 mm in three patients who remained symptom free at 11–12 month follow up along with biochemical improvement in fasting insulin and blood sugar levels [20].

EUS guided RFA may be an option not only for solid lesions but cystic pancreatic neoplasms as well. A recent prospective multicenter study involving 6 patients undergoing RFA of pancreatic cystic neoplasms showed complete resolution of PCNs in 33%, or two patients and 48.4% reduction in size in three other patients [21].

Further research should involve prospective studies recruiting more number of patients and follow them up for a longer duration to assess the true efficacy of EUS-RFA.

7. EUS guided microforceps biopsy of pancreatic cystic and solid neoplasms

Tissue biopsy remains the gold standard for an accurate pathologic diagnosis. However, limitations of technology meant that endosonographers have to rely on aspiration of cellular elements at FNA for more than two decades or on core biopsies. Developments in device miniaturization may change the current standard approach. Recently developed miniforceps (Moray, US Endoscopy, Ohio, USA and Endoflex GmbH, Voerde, Germany) can pass through the lumen of a 19 G FNA needle may allow better tissue acquisition. A few recent case reports have shown promise where mucinous pancreatic neoplasms were diagnosed on the basis of tissue biopsy of pancreatic cysts using microforceps [22–24]. More studies will clearly be needed but this is a welcome development.

8. Which gastroenterology society guidelines should one follow for pancreatic cystic lesion management and follow up?

The working group of the eleventh congress of the International Association of Pancreatology held in Sendai, Japan in 2004 came up with guidelines, informally referred to as the 'Sendai Criteria' in endoscopy parlance. These were updated in 2012, and are aptly called the International Consensus guidelines, rather than evidence-based guidelines since the level of evidence on the recommendations was low. These are commonly referred to as the 'Fukuoka guidelines'. A detailed discussion on these guidelines is beyond the scope of this commentary, but these briefly defined three 'high risk stigmata' which include obstructive jaundice, enhancing solid component a cyst and main pancreatic duct diameter >10 mm and five 'worrisome features' which include cyst >3 cm, thickened or enhancing cyst walls, main duct size (5–9) mm, non-enhancing mural nodule and abrupt change in caliber of pancreatic duct with distal pancreatic atrophy [25].

The 2012 Fukuoka International Consensus Guidelines have been lauded by several subsequent studies. A retrospective study from Japan from 2014 showed that multivariate analysis identified obstructive jaundice (OR = 23.9; $P < 0.0001$), abrupt change in MPD diameter (OR = 3.01; P = 0.017) and lymphadenopathy (OR = 5.84; P = 0.027) as independent predictive factors, with an accuracy of 69.8, 67.4, and 66.3%, respectively [26].

Surgical literature from Singapore from 2014 shows that the PPV of the high risk criteria for detecting HGD or carcinoma was 62.5% and the NPV of the low risk group was 100% [27].

The American Gastroenterology Association also recently proposed practice guidelines on management of PCNs [28]. These however have come under criticism because of a lack of distinction between mucinous cystadenomas and IPMNs, discontinuation of surveillance and lack of use of molecular markers [29]. Not enough studies are available yet that can validate the AGA guidelines fully. In our opinion, until more data becomes available, a judicious approach in keeping with the Fukuoka guidelines and consideration of patient's age, comorbidities, family history of pancreatic cancer or other genetic cancer syndromes and locally available endoscopy and surgical expertise is advised.

9. Conclusions

Pancreatic cystic and neoplasms are being diagnosed with increasing frequency [30]. Accurate diagnosis and determination of benign versus malignant lesions is crucial for determining need for surveillance versus surgery or endoscopic therapy as well as avoiding unnecessary surgery in cysts with no malignant potential. Tumor markers such as KRAS and GNAS hold promise, but which molecular marker or a combination of markers is most useful and cost effective remains to be seen. Advanced imaging with confocal laser endomicroscopy can serve as an optical biopsy and play a part in the diagnostic algorithm. Microforceps aided biopsy of pancreatic cyst wall and tumor contents hold great promise as they allow direct tissue acquisition. Much progress has been made in the role of EUS guided evaluation of pancreatic cystic neoplasms over the last several years [31], and with the advances enumerated above, the future is more than just a few shades of gray.

Future studies should include prospective multi-arm trials of microforceps biopsy versus conventional EUS-FNA and use of biochemical and molecular markers, confocal laser endomicroscopy or a combination thereof to determine best approach to pancreatic cystic neoplasms. In Osler's words, 'Medicine is a science of uncertainty and an art of probability'. Incorporation of advanced imaging and molecular markers into a new diagnostic algorithm with subsequent validation through retrospective and prospective studies has the potential to increase diagnostic accuracy and guide optimal management of patients and improve outcomes.

Conflict of interest statement

We declare that we have no conflict of interest.

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