Diagnostic and therapeutic endoscopic approaches to intraductal papillary mucinous neoplasm

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Abstract

Pancreatic cystic lesions are increasingly identified on routine imaging. One specific lesion, known as intraductal papillary mucinous neoplasm (IPMN), is a mucinous, pancreatic lesion characterized by papillary cells projecting from the pancreatic ductal epithelium. The finding of mucin extruding from the ampulla is essentially pathognomonic for diagnosing these lesions. IPMNs are of particular interest due to their malignant potential. Lesions range from benign, adenomatous growths to high-grade dysplasia and invasive cancer. These mucinous lesions therefore require immediate attention to determine the probability of malignancy and whether observation or resection is the best management choice. Unresected lesions need long-term surveillance monitoring for malignant transformation. The accurate diagnosis of these lesions is particularly challenging due to the substantial similarities in morphology of pancreatic cystic lesions and limitations in current imaging technologies. Endoscopic evaluation of these lesions provides additional imaging, molecular, and histologic data to aid in the identification of IPMN and to determine treatment course. The aim of this article is to focus on the diagnostic and therapeutic endoscopic approaches to IPMN.

Key words: Intraductal papillary mucinous neoplasm; Pancreatic cyst; Endoscopic ultrasound; Cyst; Mucinous cystic neoplasm; Mucinous cystic lesion; Pancreas

INTRODUCTION

Pancreatic cystic lesions are increasingly identified with the widespread use of state-of-the-art imaging. In particular, intraductal papillary mucinous neoplasms (IPMNs) have become a major clinical focus as a result of their increased identification and our modest understanding of their long term natural history. IPMNs are mucinous lesions that arise from the epithelial lining of the main pancreatic duct or its side branches and are characterized by neoplastic, mucin-secreting, papillary cells projecting from the pancreatic ductal surface. IPMNs range from premalignant lesions with low-grade dysplasia to invasive malignancy. Clinically, patients may present with recurrent abdominal pain, nausea, or vomiting from pancreatitis, but IPMNs are mucinous lesions that arise from the epithelial lining of the main pancreatic duct or its side branches and are characterized by neoplastic, mucin-secreting, papillary cells projecting from the pancreatic ductal surface. IPMNs are most commonly asymptomatic and discovered incidentally on routine imaging. Diagnosis of IPMN with multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI) is frequently used, but still has limitations in distinguishing main duct from branch duct type IPMN (BDIPMN) and in differentiating the broad spectrum of pancreatic cystic lesions. Endoscopic evaluation of these lesions provides additional imaging, molecular, and histologic data to aid in the identification of IPMN.
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**DIAGNOSTIC APPROACHES TO INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM**

**Endoscopic retrograde cholangiopancreatography**

In the past, endoscopic retrograde cholangiopancreatography (ERCP) was used as the gold standard imaging tool for the diagnosis of IPMN. Characteristic findings at ERCP include a dilated main pancreatic duct with mucinous filling defects. Today, high resolution MDCT, MRCP, and endoscopic ultrasound imaging have replaced the routine use of ERCP alone. While ERCP can accurately assess ductal communication, there are cases where cystic side branches do not fill with contrast due to mucus plugging and an incorrect diagnosis is made. In some cases a bulging ampulla, sometimes referred to as ‘fish-eye’ ampulla, is seen extruding thick mucin and this is virtually pathognomonic of IPMN. Despite its diminishing role in the diagnosis of IPMN, ERCP, ERC maintains a principal advantage by permitting cytological sampling of suspected IPMN and facilitating evacuation of mucin from plugged pancreatic ducts. In addition, ERCP has many potential applications as a platform for endoscopic technologies under current development.

**Endoscopic ultrasound**

Endoscopic ultrasound (EUS) has been increasingly used to identify and characterize suspected IPMNs among other pancreatic cystic lesions. Aithal et al\[9\] demonstrated that EUS can be a useful tool in determining the presence of IPMN and that characteristic imaging features such as dilated pancreatic duct, cysts, and pancreatic atrophy were seen more commonly in patients with IPMN versus patients with chronic pancreatitis. EUS had a sensitivity and specificity of 86% and 99% respectively in the detection of IPMN. The ability of EUS to discriminate benign from malignant IPMNs has been shown to have a sensitivity of 75%-90% and a specificity of 71%-91%\[8,9\]. In order to better discriminate benign from malignant neoplasms, Sai et al\[11\] proposed pancreatic-duet lavage cytology of BDIPMNs. Endoscopic retrograde pancreatoscopy was performed to identify an area of ectatic side branches. A specially designed 5F double lumen cytology catheter was next introduced into the pancreatic duct over an existing guidewire and advanced to the dilated side branch. Saline solution was instilled in small volumes then aspirated and the fluid sent for cytological evaluation. The technique had a sensitivity of 78% and specificity of 93% and may provide a preoperative tool to help reduce unnecessary pancreatic surgery in patients with benign lesions that might otherwise meet current criteria for resection.

**Peroral pancreatoscopy**

Pancreatoscopy involves the introduction of a small caliber endoscope, via a duodenoscope, into the pancreatic duct to directly observe the ductal epithelium. The characteristic findings of IPMN include a papillary tumor with ‘fish-egg’ like appearance, granular mucosa, or mucin\[10\]. Filling defects seen on ERCP suggestive of a pancreatic stone or main duct IPMN can be differentiated with peroral pancreatoscopy (POPS) and this permits biopsy of the pancreatic duct for histopathologic review. In one study, POPS alone was found to have a sensitivity of 100% in differentiating benign from malignant main duct IPMN, although the sensitivity was poor, 43% for BDIPMN\[17\]. Preoperatively, POPS can aid in surgical planning by delineating the extent of pancreatic ductal disease and identifying surgical margins (i.e. helping to regionalize a main duct IPMN) through direct visualization of the pancreatic duct epithelium and site-directed biopsy\[10,18,19\].

**Intraductal ultrasound**

Intraductal examination of the main pancreatic duct and surrounding structures using high frequency ultrasound probes has been demonstrated. Harani et al\[17\] showed that intraductal ultrasound (IDUS) alone has a better sensitivity and specificity for differentiating benign from malignant BDIPMNs (sensitivity 77% and specificity 100%) versus the main duct type (sensitivity 56% and specificity 71%). The combined use of POPS and IDUS resulted in the greatest accuracy (88%) for differentiating neoplastic...
lesions when compared to the use of CT, EUS, POPS, or IDUS alone. However, one group reported a respective sensitivity and specificity of 94% and 29% for the ability of IDUS to differentiate neoplastic from non-neoplastic lesions [10]. Taking into account size, Yasuda et al [19] showed that IDUS had a sensitivity of 100% for detecting protruding polypoid lesions higher than 3 mm in the pancreatic duct.

### Narrow band imaging

The use of narrow band imaging (NBI) in examining ductal pancreatic lesions is limited. NBI functions by narrowing the spectral bandwidth of red-green-blue optical filters and thus emphasizes mucosal structures. NBI has been combined with POPS in a case series study of patients with IPMN and the results indicated improved visualization of the pancreatic duct surface structures and microvessels [20] (Figure 1). The improved visualization permits targeted sampling of extraordinarily small lesions. However, the technology is limited to patients with dilated pancreatic ducts and directed biopsies can be challenging given the tortuousness of the pancreatic duct.

### Optical coherence tomography

Optical coherence tomography (OCT) is a probe-based imaging modality that provides micrometer resolution images of duct epithelium. Studies of solid lesions using pancreatic intraductal OCT demonstrated its feasibility and its superiority to brush cytology in distinguishing neoplastic from non-neoplastic lesions [21,22]. Until recently, application of this novel imaging modality to pancreatic cystic lesions had never been attempted. An ex-vivo OCT study of resected pancreatic tissue specimens containing cystic lesions, including IPMNs, demonstrated a 94% accuracy for differentiating serous cystadenomas from mucinous cystic neoplasms and IPMNs [23]. Application of this technology in a catheter-based system may provide high-resolution images of the pancreatic duct and immediately surrounding structures that can be obtained at ERCP or EUS-FNA examination (Figure 2).

### ENDOSCOPIC TREATMENT OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

#### Ethanol ablation

Generally, the resection of main and mixed variant IPMNs is recommended, although the long-term natural history of BDIPMNs in particular make the timing of surgical resection difficult. Furthermore, patients with significant morbidity are precluded from surgery and therefore definitive treatment. Less invasive therapies such as chemical ablation of pancreatic cysts offer an alternative. Initial studies of cyst ethanol ablation demonstrated the feasibility and safety of this approach and the potential promise of long term cyst resolution in some patients [24].
DeWitt et al\(^3\) recently conducted a randomized, double-blind study of EUS-guided ethanol versus saline injection of pancreatic cysts. The study enrolled patients with cysts not communicating with the main duct. The participating subjects were heterogeneous and contained IPMNs, MCNs, and perhaps simple cysts among others. While the study was not specifically for IPMNs alone, the authors reported complete pancreatic cyst ablation in 33.3% of injected cysts on follow-up CT; there was a significant decrease in cyst surface area \((P = 0.009)\) in all patients who received ethanol as opposed to saline lavage. Further studies focusing on cysts with imaging morphology characteristic of BDIPMN alone are needed. The EUS 2008 working group published a document that summarized potential roles for this ablative technique and provided recommendations for areas of future research\(^2\).

**Combination therapy and other alternatives**

EUS-guided injection of ethanol/paclitaxel into the pancreas resulted in complete resolution of pancreatic cysts in 11 of 13 patients (84.6%) undergoing successful injection\(^3\). In 2 patients, partial cyst resolution was observed. The group reported acute pancreatitis in one patient. Future studies may include the testing of immunomodulatory drugs, radiopharmaceuticals, or other chemotherapeutic agents delivered in a variety of media.

**CONCLUSION**

The diagnosis of pancreatic IPMN and the decision of whether to resect or observe remains an ongoing challenge for the clinician. Significant imaging advances have helped to ensure more accurate diagnosis and better characterization of IPMNs which in turn helps guide long-term management. Current and evolving endoscopic techniques add exciting diagnostic tools to our imaging arsenal and provide a conduit for performing minimally invasive therapeutic treatments of IPMN.

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