World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i10.337

*World J Gastrointest Surg* 2010 October 27; 2(10): 337-341
ISSN 1948-9366 (online)


TOPIC HIGHLIGHT

**Elijah Dixon, MD, BSc, MSc (Epi), FRCSC, FACS, Assistant Professor,** *Series Editor*

# Diagnostic and therapeutic endoscopic approaches to intraductal papillary mucinous neoplasm

Brian G Turner, William R Brugge

Brian G Turner, William R Brugge, Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, United States
Author contributions: Turner BG and Brugge WR are solely responsible for all contributions to the article.
Correspondence to: William R Brugge, MD, Gastroenterology Unit, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, United States. wbrugge@partners.org
Telephone: +1-617-7243715 Fax: +1-617-7245997
Received: May 18, 2010 Revised: September 28, 2010
Accepted: October 5, 2010
Published online: October 27, 2010

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

**Peer reviewer:** Rungsun Rerknimitr, MD, Division of Gastroenterology, Internal Medicine, King Chulalongkorn Memorial Hospital, Rama IVC Rd Lumpini, Bangkok 10310, Thailand

Turner BG, Brugge WR. Diagnostic and therapeutic endoscopic approaches to intraductal papillary mucinous neoplasm. *World J Gastrointest Surg* 2010; 2(10): 337-341 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i10/337.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i10.337

## 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.



## INTRODUCTION

Pancreatic cystic lesions are increasingly identified with the widespread use of state-of-the-art imaging[1]. 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[2]. 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 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)[3] and in differentiating the broad spectrum of pancreatic cystic lesions[4-7]. Endoscopic evaluation of these lesions provides additional imaging, molecular, and histological 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.

## 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 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*[8] 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%[9,10]. In order to better discriminate benign from malignant neoplasms, Sai *et al*[11] proposed pancreatic-duct-lavage cytology of BDIPMNs. Endoscopic retrograde pancreatography 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.

### *Endoscopic ultrasound guided fine needle aspiration to perform molecular analysis*

The use of fine needle aspiration (FNA) to obtain cyst fluid aspirate facilitates the quantitative analysis of molecular markers such as carcinoembryonic antigen (CEA), which has been shown to be more accurate in the diagnosis of mucinous lesions than EUS and cytology[12]. Additionally, molecular analysis with the commercially available PathfinderTG can aid in preoperative diagnosis of malignant and benign mucinous pancreatic cysts[13]. A recent report of pancreatic cyst fluid DNA analysis, referred to as the PANDA study[14], demonstrated that DNA analysis diagnosed malignancy in all cases where cytology with FNA was negative. The most specific test for cystic malignancy was K-ras followed by allelic loss (96%). Additionally, K-ras mutations were associated with mucinous cystic lesions with a specificity of 96%, but sensitivity of only 45%. Pitman *et al*[15] reported that cyst fluid analysis in BDIPMNs less than 3 cm added enhanced diagnostic capabilities when the criteria of CEA > 2500 ng/mL or atypical epithelial components seen on cytology were found. In practice, it is likely that a combined approach to cyst fluid analysis will ultimately be the most diagnostic. The combination of CEA and molecular analysis has been shown to have a 100% sensitivity for diagnosing mucinous cysts; however, CEA level did not correlate well with the quantity of DNA[16].

### *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. Hara *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

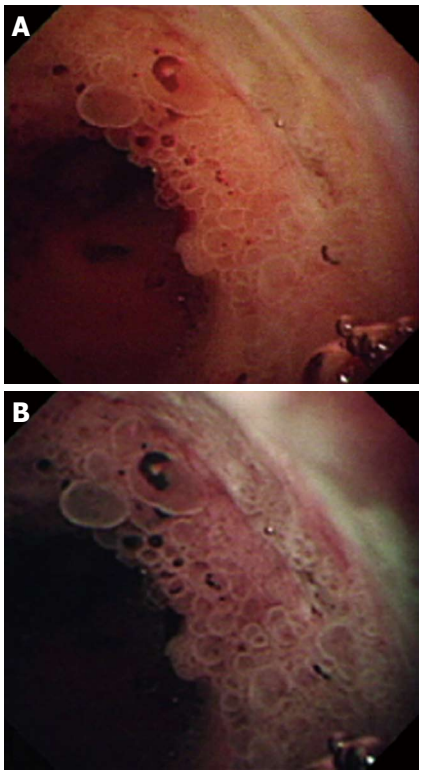


**Figure 1 Peroral pancreatoscopy images.** A: Peroral pancreatoscopy of the main pancreatic duct demonstrating the presence of papillary tumor; small, ovoid papillary projections can be seen; B: The same projections are pictures here under observation with narrow band imaging; the surface structure of the lesions is much better visualized. (The figure is from Itoi *et al*[20] and reproduced with permission from *Elsevier Inc*.)

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

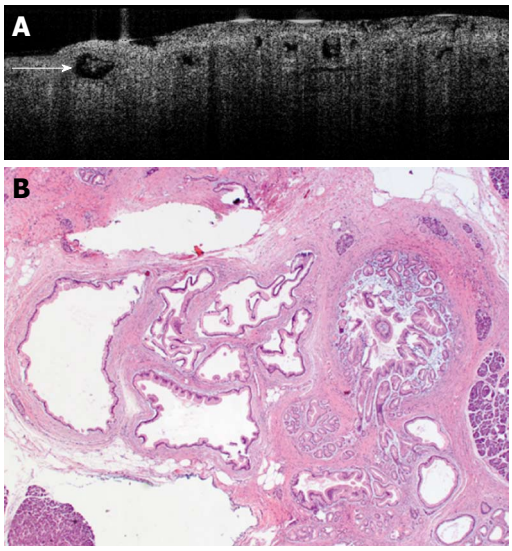


**Figure 2 An optical coherence tomography image of a patient with borderline intraductal papillary mucinous neoplasm (A) and photomicrograph of an intraductal papillary mucinous adenoma in the same patient (B).** A: Multiple cystic lesions are pictured here with medium to high scattering in the cyst cavity; the scattering suggests the existence of mucin. A single, mucinous cystic lesion is indicated by the white arrow and scattering is clearly seen within the cystic structure. Image provided courtesy of Dr. Sevde Cizginer at Massachusetts General Hospital, Boston, MA: B: Photomicrograph of an intraductal papillary mucinous adenoma in the same patient. The cysts are lined by a single layer of foveolar-type epithelial cells. Focally, papillary areas are identified. Image provided courtesy of Dr. Vikram Deshpande at Massachusetts General Hospital, Boston, MA.

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 mucionous 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*[25] 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[26].

### 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[27]. 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.

## REFERENCES


1 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807

2 **Adsay NV**. Cystic neoplasia of the pancreas: pathology and biology. *J Gastrointest Surg* 2008; **12**: 401-404

3 **Song SJ**, Lee JM, Kim YJ, Kim SH, Lee JY, Han JK, Choi BI. Differentiation of intraductal papillary mucinous neoplasms from other pancreatic cystic masses: comparison of multirow-detector CT and MR imaging using ROC analysis. *J Magn Reson Imaging* 2007; **26**: 86-93

4 **Chaudhari VV**, Raman SS, Vuong NL, Zimmerman P, Farrell J, Reber H, Sayre J, Lu DS. Pancreatic cystic lesions: discrimination accuracy based on clinical data and high resolution CT features. *J Comput Assist Tomogr* 2007; **31**: 860-867

5 **Fisher WE**, Hodges SE, Yagnik V, Morón FE, Wu MF, Hilsenbeck SG, Raijman IL, Brunicardi FC. Accuracy of CT in predicting malignant potential of cystic pancreatic neoplasms. *HPB* (Oxford) 2008; **10**: 483-490

6 **Gerke H**, Jaffe TA, Mitchell RM, Byrne MF, Stiffler HL, Branch MS, Baillie J, Jowell PS. Endoscopic ultrasound and computer tomography are inaccurate methods of classifying cystic pancreatic lesions. *Dig Liver Dis* 2006; **38**: 39-44

7 **Procacci C**, Biasiutti C, Carbognin G, Accordini S, Bicego E, Guarise A, Spoto E, Andreis IA, De Marco R, Megibow AJ. Characterization of cystic tumors of the pancreas: CT accuracy. *J Comput Assist Tomogr* 1999; **23**: 906-912

8 **Aithal GP**, Chen RY, Cunningham JT, Durkalski V, Kim EY, Patel RS, Wallace MB, Hawes RH, Hoffman BJ. Accuracy of EUS for detection of intraductal papillary mucinous tumor of the pancreas. *Gastrointest Endosc* 2002; **56**: 701-707

9 **Pais SA**, Attasaranya S, Leblanc JK, Sherman S, Schmidt CM, DeWitt J. Role of endoscopic ultrasound in the diagnosis of intraductal papillary mucinous neoplasms: correlation with surgical histopathology. *Clin Gastroenterol Hepatol* 2007; **5**: 489-495

10 **Yamao K**, Nakamura T, Suzuki T, Sawaki A, Hara K, Kato T, Okubo K, Matsumoto K, Shimizu Y. Endoscopic diagnosis and staging of mucinous cystic neoplasms and intraductal papillary-mucinous tumors. *J Hepatobiliary Pancreat Surg* 2003; **10**: 142-146

11 **Sai JK**, Suyama M, Kubokawa Y, Watanabe S, Maehara T. Pancreatic-duct-lavage cytology in candidates for surgical resection of branch-duct intraductal papillary mucinous neoplasm of the pancreas: should the International Consensus Guidelines be revised? *Gastrointest Endosc* 2009; **69**: 434-440

12 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336

13 **Shen J**, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer Cytopathol* 2009; **117**: 217-227

14 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102

15 **Pitman MB**, Michaels PJ, Deshpande V, Brugge WR, Bounds BC. Cytological and cyst fluid analysis of small (< or =3 cm) branch duct intraductal papillary mucinous neoplasms adds value to patient management decisions. *Pancreatology* 2008; **8**: 277-284

16 **Sawhney MS**, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, Brown A, Chuttani R, Pleskow DK. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; **69**: 1106-1110

17 **Hara T**, Yamaguchi T, Ishihara T, Tsuyuguchi T, Kondo F, Kato K, Asano T, Saisho H. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology* 2002; **122**: 34-43

18 **Atia GN**, Brown RD, Alrashid A, Halline AG, Helton WS, Venu RP. The role of pancreatoscopy in the preoperative evaluation of intraductal papillary mucinous tumor of the pancreas. *J Clin Gastroenterol* 2002; **35**: 175-179

19 **Yasuda K**, Sakata M, Ueda M, Uno K, Nakajima M. The use of pancreatoscopy in the diagnosis of intraductal papillary mucinous tumor lesions of the pancreas. *Clin Gastroenterol Hepatol* 2005; **3**: S53-S57

20 **Itoi T**, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Arisaka Y, Moriyasu F. Initial experience of peroral pancreatoscopy combined with narrow-band imaging in the diagnosis of intraductal papillary mucinous neoplasms of the pancreas (with videos). *Gastrointest Endosc* 2007; **66**: 793-797

21 **Testoni PA**, Mangiavillano B, Albarello L, Mariani A, Arcidiacono PG, Masci E, Doglioni C. Optical coherence tomography compared with histology of the main pancreatic duct structure in normal and pathological conditions: an 'ex vivo

study'. *Dig Liver Dis* 2006; **38**: 688-695
22 **Testoni PA**, Mariani A, Mangiavillano B, Arcidiacono PG, Di Pietro S, Masci E. Intraductal optical coherence tomography for investigating main pancreatic duct strictures. *Am J Gastroenterol* 2007; **102**: 269-274
23 **Cizginer S**, Deshpande V, Iftimia N, Karaca C, Brugge WR. Optical Coherence Tomography (OCT) Imaging Can Detect Fine Morphologic Features of Pancreatic Cystic Neoplasms and Differentiate Between Mucinous and Non-Mucinous Cysts. *Gastroenterology* 2009; **136**: A-45
24 **Gan SI**, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc* 2005; **61**: 746-752
25 **DeWitt J**, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc* 2009; **70**: 710-723
26 **Ho KY**, Brugge WR. EUS 2008 Working Group document: evaluation of EUS-guided pancreatic-cyst ablation. *Gastrointest Endosc* 2009; **69**: S22-S27
27 **Oh HC**, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 2008; **67**: 636-642

**S- Editor** Wang JL **L- Editor** Hughes D **E- Editor** Yang C