13 Endoscopic Retrograde Cholangiopancreatography (ERCP): Pancreatoscopy for the Evaluation of Pancreatic Neoplasia

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Peroral Pancreatoscopy Equipment and Technique

Peroral pancreatoscopy was first described in Japan in 1975 [1]. The usefulness of this technique was limited by poor optics and instrument fragility as well as the relatively large diameter of the instrument compared to the main pancreatic duct (MPD) diameter.

Types of Pancreatoscopes

In the United States, pancreatoscopy is currently performed with scopes and catheters designed for inspection of the bile duct. The limitation inherent with pancreatic duct inspection is its relatively narrower caliber compared to the bile duct. Initial iterations of devices specific to the pancreatic duct were primarily developed in East Asia. Prototypes included optical image fiber bundles and ultrathin pancreatoscopes without a working channel or an ability to perform tip deflection. Current prototype and commercially available pancreatoscopes have improved optical resolution and working channels, but limitations of diameter, fragility, and tip deflection to negotiate tortuous ducts and strictures remain. Although slim endoscopes may be used for direct POP, this procedure is primarily performed in conjunction with a duodenoscope. The devices used for pancreatoscopy include prototype video pancreatoscopes with narrow-band imaging (NBI) or autofluorescence imaging (AFI), and commercially available choledochoscopes with two-way tip deflection and a single 1.2-mm working channel for irrigation and biopsy forceps introduction (Olympus, Inc. and Pentax, Inc.). Also, the semidisposable catheter-based SpyGlass Direct visualization™ (Boston Scientific, Inc.) system is FDA-approved for pancreatic duct inspection and has a four-way tip deflection, a dedicated 1.2-mm working channel diameer, two 0.6-mm irrigation ports, and a lumen for the reusable optical probe [2–4]. A detailed review of the available cholangiopancreaotoscopes has been summarized in a technical status evaluation report by the American Society of Gastrointestinal Endoscopy's Technology committee and other technical reviews [5, 6]. It should be noted that to perform pancreatoscopy, significant experience with pancreatic endotherapy is a suggested baseline requirement.

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Patient Preparation and Pancreatic Duct Access

Prophylactic IV antibiotics are administered preprocedurally. We utilize general anesthesia due to the need for saline irrigation during ductal inspection and potential for reflux of fluid into the stomach. These procedures also tend to be longer than conventional pancreatic endotherapy cases. The patient is placed in the semiprone position. Following ductal access with a 0.035-in. coated guidewire advanced typically beyond the target lesion, endoscopic sphincterotomy is performed in preparation for pancreatoscopy. If the pancreatic duct orifice is patulous, as may be seen in patients with main-duct intraductal papillary mucinous neoplasia (IPMN), endoscopic sphincterotomy prior to pancreatoscope introduction may not be necessary. Jung et al. [7] performed endoscopic pancreatic sphincterotomy in 18 patients prior to pancreatoscopy. One complication (bleeding) was reported. Ueno et al. [8] performed endoscopic sphincter dilation in patients with IPMN. This latter technique has the theoretical advantage of preserving the sphincter function of the papilla. The authors observed significant hyperamylasemia after endoscopic sphincter dilation and recommended temporary pancreatic stenting. This, however, may not be necessary in patients with main-duct IPMN. Further, a large mucin burden may rapidly occlude small-diameter stents and result in postprocedural pancreatitis (personal observation). The prototype ultrathin pancreatoscopes have permitted device introduction in nondilated MPD. Kodama et al. [9] reported a series of 36 chronic pancreatitis patients with a technical success of 90 %, but its clinical utility without the ability to perform directed tissue sampling remains to be seen.

Commercially available pancreatoscopes are of larger diameter (approximately 10 F). The angle to the pancreatic orifice from the duodenoscope is more oblique than compared to the bile duct and initial transpapillary advancement is often simpler than traversing the biliary orifice, which is often at a right angle. Difficulty, however, may be encountered when advancing a 10 F device through tortuous segments such as the genu or narrowings that are not always suspected on pancreatography. Dilation with a 4- or 6-mm balloon prior to attempting device introduction may be required.

Technique Description

Pancreatoscopy may be feasible through the major or minor papilla, with the latter being technically challenging because of more acute angulation during device introduction, limited maneuverability, and endoscope stability [10, 11]. The endoscope-based two-operator (e.g., "mother–daughter") system requires an endoscopist and a trained assistant, who may be a nurse, technician, or second endoscopist to control suction and tip deflection at the handle. Further, the assisting provider is also tasked with the important aspect of minimizing angulations and torsion of the exposed shaft along its length from the handle of the pancreatoscope to its entry into the working channel cap of the duodenoscope. The pancreatoscope is advanced over an indwelling guidewire ideally beyond the target, followed by guidewire withdrawal for mucosal inspection and to improve irrigation with sterile saline to aid visualization. During intraductal inspection, due to an inherent acute angulation at the relatively fixed genu, circumferential inspection of this area tends to be limited but may be enhanced by torqueing of the duodenoscope and tip deflection of the pancreatoscope. For the single-operator catheter-based system, the control section knobs should be unlocked and the optical probe is preloaded into the disposable access catheter and advanced to within a few millimeters of the tip of the catheter. Following advancement to the target and guidewire withdrawal, the optical probe is gently advanced beyond the catheter tip for intraductal inspection. The endoscopist has control of the four-way steering dials and may periodically lock the dials for fine movements of the catheter to stabilize visualization of a target during tissue acquisition using miniature forceps biopsy.

Techniques to Improve Visualization

Irrigation rates should be kept as low as possible to permit a sufficient view and to potentially reduce the risk of pancreatitis. Periodic suctioning of duodenal contents in the setting of a sphincterotomy and aspiration using the pancreatoscope is encouraged. For the catheter-based system, a Y-adapter may be connected to the working channel of the control section to permit suctioning, and this preserves other working channel functionality such as biopsy. The endoscope-based system has suction capability. Other techniques used to optimize visualization include the use of mucomyst, which we have not found consistently useful; a "closed circuit" technique of irrigation and suctioning in the catheter-based system to reduce debris obscuring visualization; and the administration of intravenous secretin has been described to stimulate pancreatic juice flow [12].

Sampling Techniques

To facilitate insertion of accessories, such as biopsy forceps or electrohydraulic (EHL) probe, the elevator of the duodenoscope needs to be relaxed and the angulation of both the duodenoscope and the pancreatoscope need to be reduced. If passage of the biopsy forceps is possible through the accessory channel, POP-directed biopsies can be obtained. If the target lesion is closer to the pancreatic orifice (e.g., pancreatic head), then passage of the miniature forceps may not be feasible. In this scenario, or if additional sampling is desired using pediatric or biliary forceps, POP-assisted biopsies can be obtained. With this technique, reference to a fluoroscopic spot film obtained of the position of the pancreatoscope at the target lesion guides tissue sampling through the accessory channel of the duodenoscope [13].

Intraoperative Pancreatoscopy

The selective use of intraoperative pancreatoscopy to evaluate the MPD appears to help to enable the surgeon to guide resection margins. We are unaware, however, of this being routinely utilized in the United States. Kaneko et al. [14] reported a sensitivity, specificity, and overall accuracy of intraoperative pancreatoscopy of 100 % for the diagnosis of IPMN and defining the extent of tumor involvement in the duct. Pucci et al. [15] reported the use of intraoperative pancreatoscopy in 23 pancreatic resections; 18 of these operations were performed for presumed main-duct IPMN, and in 5 (22 %), the surgical resection was extended as a result of the pancreatoscopy findings.

Adverse Events

Adverse events from cholangiopancreatoscopy may be more than double those of endoscopic retrograde cholangiopancreatography (ERCP) alone (7 % vs. 2.9 %). Cholangiopancreatoscopy appears to be associated with similar rates of pancreatitis when compared to ERCP being performed without cholangiopancreatoscopy [16]. It is likely, however, that higher rates of pancreatitis may be seen that is inherent to pancreatic endotherapy, in general, rather than the use of pancreatoscopy itself [10].

Pancreatic Carcinoma in situ

Often, pancreatic cancers are locally advanced or metastatic at the time of diagnosis. Efforts to improve pancreatic cancer survival rates include early-stage detection, such as carcinoma in situ, which are typically difficult to locate by conventional diagnostic methods such as CT, EUS, and ERCP. Limited data exist on this indication, and in general, the literature for detecting adenocarcinoma of the pancreas utilizing pancreatoscopes includes electronic devices that are prototypes or that are not currently under development.

In a small series of 11 patients, POP and pancreatoscopic cytology were utilized to identify pancreatic carcinoma in situ in a select cohort of patients [17]. POP was utilized preoperatively with identification of ten main duct and one side-branch neoplasm. POP mucosal findings included

papillary projections, irregular margins, or a nodular appearance. Using pancreatoscopy-guided aspiration and cytology, malignant cells were obtained from all lesions in the MPD, while conventional pancreatic juice cytology was diagnostic in 60 % of the cases.

Invasive Pancreatic Cancer

EUS has been suggested as the most useful modality for the diagnosis of pancreatic cancer [18]. However, in some patients a discrete mass cannot be delineated within a stenotic ductal segment because of concomitant pancreatitis, for example, and POP with an ultrathin fiberscope may be useful [19]. One issue is that most pancreatic cancers seem to originate within side branches and pancreatoscopy may only observe neoplastic changes when these progress to involve the main duct, limiting its usefulness in the detection of early cancers [20]. In an attempt to overcome this limitation, a prototype 2.2-mm-diameter fiberscope equipped with a shape-memory alloy has been developed. The tip of this fiberscope can be curved freely by heating the alloy with a controller [21]. Tajiri et al. [22] developed a special video converter connected to the head of the pancreatoscope to permit visualization of sequential electronic endoscope images on a monitor. They performed examinations with this system in 52 cases (8 with pancreatic cancer, 19 with chronic pancreatitis, and 25 normal cases); however, we are unaware if current iterations of this technology are available even in the prototype stage.

Peroral Pancreatoscopy Findings in Patients with Pancreatic Cancer

Pancreatoscopy findings in pancreatic cancer include nonspecific descriptors such as coarse mucosa, erythema, and friability and more specific lesions such as protrusions or an infiltrative stricture (e.g., near-occlusion of the lumen) with irregular margins (see Fig. 13.1). Although coarse mucosa and friability are substantially more frequent in pancreatic cancer than in benign ductal stenosis, these are not specific for neoplasia and a lack of standardization of terms has limited widespread applicability when comparing the literature. In a large series of 115 cases of pancreatic diseases, findings specific to pancreatic cancer included protrusion, friability, and tumor vessels, which were particularly associated with small (<2 cm) pancreatic cancers [19].

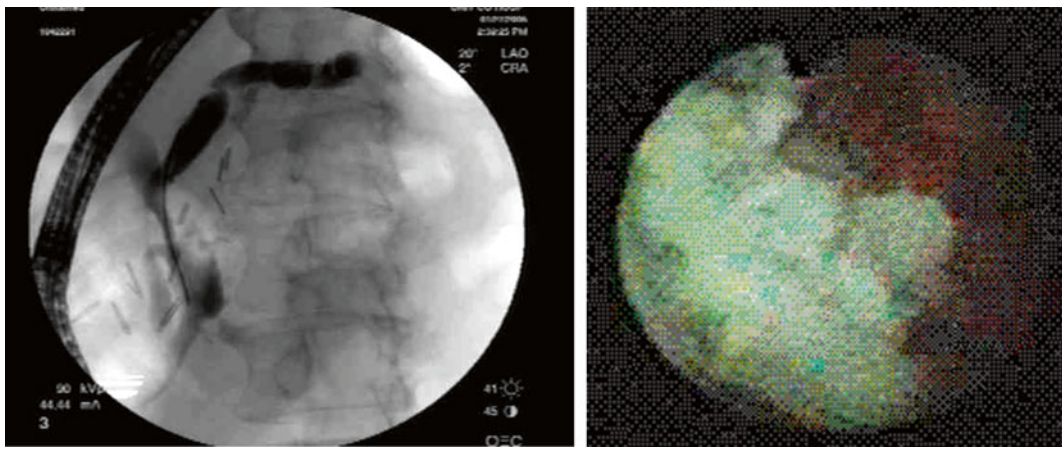

Fig. 13.1 (**a**) Pancreatogram with pancreatic head stricture; (**b**) fiber optic pancreatoscopy of an ulcerated intraductal mass positive for adenocarcinoma

Intraductal Papillary Mucinous Neoplasia

IPMN of the pancreas is an increasingly detected clinical entity characterized by papillary hyperplasia of the pancreatic ductal epithelium, excessive mucin secretion, and cystic dilation of the pancreatic duct. The pathologic abnormalities may involve the entire MPD, a segment of the MPD, multiple segments of the MPD (multifocal IPMN), only the side branches (SB-IPMN), or both MPD and SB (mixed-IPMN) [23].

Because IPMN constitutes a potentially malignant, premalignant, or malignant condition at the time of diagnosis, an accurate definition of disease extent and tissue sampling are paramount to the appropriate management of IPMN [24]. A variety of imaging techniques such as computed tomography (CT scan) of the abdomen, ERCP, endoscopic ultrasound (EUS), and magnetic resonance cholangiopancreatography (MRCP) are currently used. In a small series, when compared to ERCP and MR-virtual pancreatography (MR-VP), computed tomography virtual pancreatoscopy (CT-VP) and three-dimensional (3D) CT pancreatographic images were finer in quality, and the procedures were less invasive, faster, and less expensive [25]. In an early selective series of 47 patients with IPMN who had undergone surgical resection, the overall accuracy of CT, ERCP, and EUS in distinguishing between invasive and noninvasive tumors was 76 %, 79 %, and 76 %, respectively [26]. In an effort to improve the endoscopic detection of IPMN, various analyses of pancreatic juice cytology [27], K-ras gene mutations [28], and telomerase activity [29] have been proposed. Although diagnostic ERCP is often not required in order to secure the diagnosis of IPMN, pancreatic juice cytology may provide a simple method to evaluate IPMN, though it also remains with limited sensitivity. In a series of 103 resection patients with IPMN (29 adenomas, 17 borderline, 25 carcinoma in situ, and 32 invasive carcinoma), pancreatic juice was collected with a catheter in 71 patients and by POP in 32 patients [30]. The sensitivity for the detection of IPMN was 62.2 % when pancreatic juice was collected by POP and was 38.2 % when it was collected using a catheter—and this was despite a highly select group of neoplastic patients. Interestingly, for pancreatic carcinoma, the sensitivity of pancreatic juice cytology was only 25.4 %, which was significantly lower than for POP-assisted collection of pancreatic juice in detecting IPMN (68.2 %). This may be related to the fact that ductal adenocarcinoma strictures are more difficult to traverse and perhaps cytology from juice obtained downstream of the stricture may have limited tumor cells.

Pancreatoscopy Findings in Intraductal Papillary Mucinous Neoplasia

A key study was performed by Hara et al. [31], who performed a retrospective review of their experience in evaluating patients with IPMN by and intraductal ultrasound (IDUS) over a 13-year period. Sixty consecutive IPMN patients were included in this study (Fig. 13.2). The authors assessed tumor type (elevated vs. excavated), morphology per POP (type I: granular; type II: fish-egg-like without vascular images; type III: fish-egg-like with vascular images; type IV: villous type; and type V: vegetative type) (Figs. 13.3, 13.4 and 13.5), maximum tumor height as determined by IDUS, and tumor extent (head vs. body vs. tail; MPD vs. SB). Results obtained with POP and IDUS were correlated and compared with surgical pathology serving as the gold standard. The ability of CT, EUS, and K-ras point mutations in pancreatic juice to distinguish benign (hyperplasia or adenoma) from malignant (carcinoma in situ or invasive carcinoma) IPMN was also studied. A high proportion (40/60, 67 %) had protruding lesions. Most malignant tumors had a POP morphology type III, IV, or V ($p<0.0001$), with a reported sensitivity, specificity, and accuracy of 68 %, 87 %, and 75 % for differentiating benign from malignant IPMN. Maximum tumor height of protruding lesions as measured by IDUS (2.27 ± 1.5 mm in the benign group, and 5.96 ± 4.03 in the malignant group) was also able to discriminate benign from malignant tumors ($p<0.001$). CT and EUS had a sensitivity and accuracy ranging from 32 to 65 %. When a

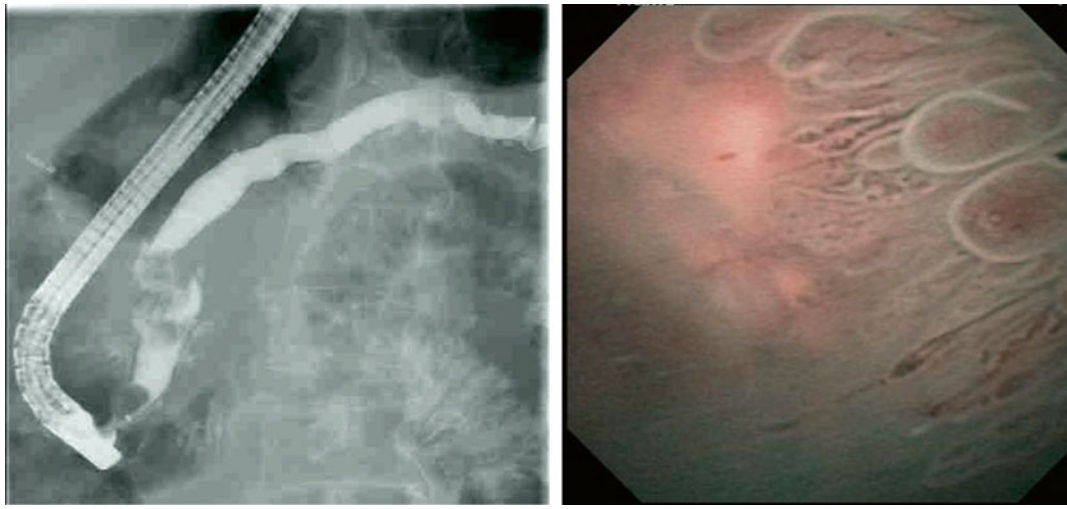

Fig. 13.2 (**a**) Pancreatogram with mucinous filling defects in the pancreatic head; (**b**) video pancreatoscopy image of Type IV villous IPMN

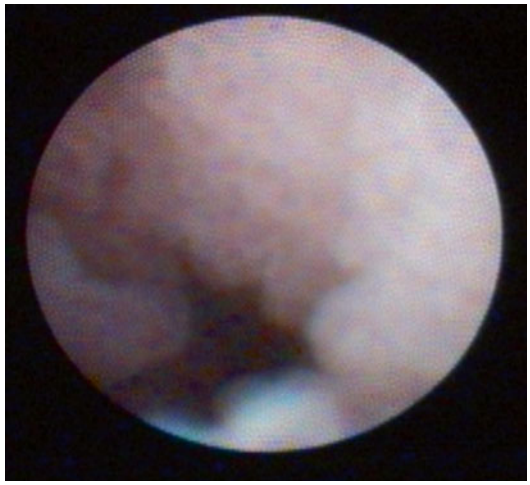

Fig. 13.3 Pancreatoscopy image of a Type 1 granular-type IPMN

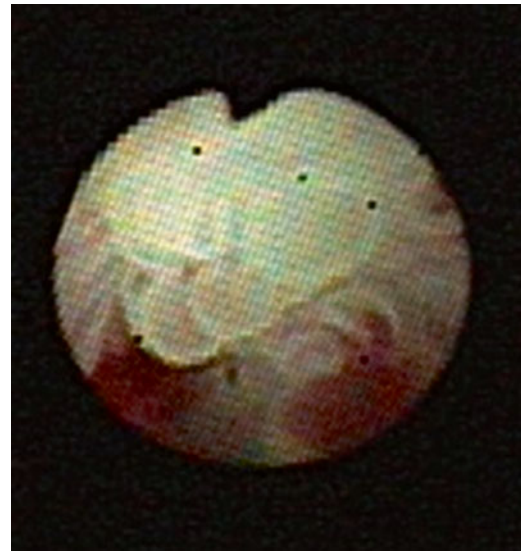

Fig. 13.4 Pancreatoscopy image of Type 2 fish-egg IPMN

positive K-ras point mutation was considered a malignant finding, the sensitivity, specificity, and accuracy reached 87 %, 15 %, and 61 %, respectively. Only one of the 60 patients resected (1.6 %) had positive surgical margins. The 3-year relapse-free and overall survival were 93 % and 95 %, respectively. Thus, POP and IDUS may help to distinguish benign from malignant IPMN, determine tumor extent, and guide therapy. The implication of these data is that these techniques may contribute to the improvement in postoperative results though the follow-up is relatively short. The authors find pancreatoscopy to be of more clinical relevance as directed tissue sampling may be performed at the same time.

Miura et al. [32] reported their experience of diagnosis of IPMN in 21 patients by means of peroral pancreatoscopy using a small-diameter videoscope (2.6-mm OD and 0.5-mm working channel) and NBI. Endoscopically, seven cases were classi-

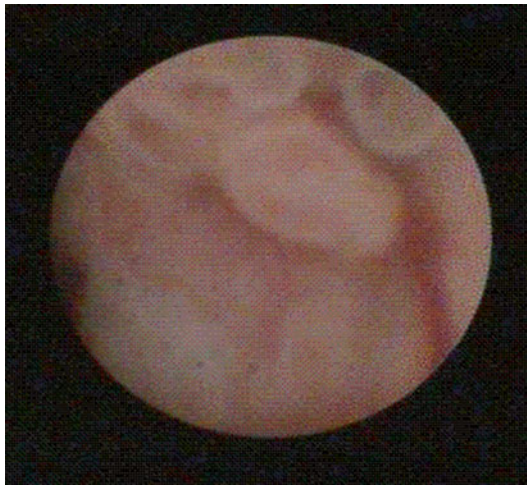

Fig. 13.5 Fiber optic pancreatoscopy image of a Type V vegetative IPMN

fied as villous (Type IV) and two cases as vegetative (Type V), and nine cases were diagnosed as adenocarcinoma. Ten cases with "sessile" type or "semi-pedunculated" type were diagnosed as adenoma or hyperplasia. The distinction between "sessile" and "vegetative" types was not entirely clear. Subjectively, vascular patterns and protrusions were detected more clearly in the NBI images than under white light observation.

In a series of 24 patients with suspected IPMN referred for surgery, intraoperative pancreatoscopy using an ultrathin pancreatoscope detected ten cases of intraductal IPMN lesions that could not be detected by preoperative EUS or ERCP; IPMN is defined in the latter group to include a well-defined filling defect of polypoid tumor by pancreatography. Five of the ten cases were intraductal multicentric lesions [14]. For the diagnosis of IPMN, the sensitivity, specificity, and overall accuracy of intraoperative pancreatoscopy were all 100 %; respective values were 43.8 %, 100 %, and 60.9 % for ERCP without POP and 47 %, 100 %, and 62.5 % for EUS. Intraoperative pancreatoscopy with NBI has been reported also to be a useful adjunct for IPMN management in guiding intraoperative decision making of the resection margins [33].

An additional series of patients undergoing POP included 60 patients with surgically confirmed IPMN of whom 57 (95 %) underwent technically successful POP. POP findings included papillary projections (58 %), mucin only (23 %), granular mucosa (16 %), and coarse mucosa (4 %). As in previous series, papillary projections were more prevalent in patients with advanced histology (23 % of adenoma, 58 % of borderline malignancy, 70 % of noninvasive IPMN, and 89 % of invasive IPMN) [19]. In a smaller series of 12 patients with IPMN (11 MPD, 1 SB), the authors observed oval-shaped "fish-egg" lesions in ten patients and nodular or villous changes in two patients. The patients with invasive IPMN consisted of the oval-shaped tumors with erythema or villous tumors and dilated blood ("tumor") vessels. In the one case of SB-IPMN, POP observed papillary projections spreading from the orifice of the affected side branch [12].

Most recently, our group performed a retrospective review of POP in the evaluation of suspected MPD neoplasia over a 13-year period [34]. Seventy-eight patients underwent 103 POPs. Technical success was 98 %. Twenty-one patients were diagnosed with MD-IPMN (6 dysplastic, and 15 nondysplastic), and five patients with SB-IPMN. POP was useful in localizing MPD-IPMN to guide resection, excluding lesions in the head for anticipated extended pancreatic tail resection, and evaluating for mixed IPMN in patients with established SB-IPMN. Among the 6 dysplastic MPD-IPMN, POP findings included a vegetative mass Type V ($N=1$), and villous projections Type IV ($N=5$). Among the 15 nondysplastic MD-IPMN, POP findings included villous projections ($N=8$), vegetative mass ($N=3$), stricture and mucin ($N=3$), and mucin alone ($N=1$). Overall, the POP visual impression had a sensitivity, specificity, and accuracy of 91 %, 96 %, and 94 %, respectively.

Summary

Commercially available pancreatoscopes are now widely available, though significant baseline experience in not only ERCP but also pancreatic endotherapy is a necessity prior to incorporating this technology into practice. Techniques of tissue sampling include intraductal aspiration of pancreatic juice for cytology, pancreatoscopy-

directed biopsy, and pancreatoscopy-assisted biopsy. POP has a high success rate in appropriate patient populations with dilated pancreatic ducts and carries an acceptable risk profile. It is a useful adjunct to ERCP, EUS, and noninvasive imaging to improve the detection of pancreatic duct neoplasia with specific attention to IPMN. It may also be utilized to discriminate malignant from benign IPMN. Though advancements in fragility have been made, refined optics and ease of accessory device passage through the working channel are still awaiting commercial availability. With this anticipated progress in technology, POP may become more widely adapted, with an improved success and complication profile.

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