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Uptodate in the assessment and management of intraductal papillary mucinous neoplasms of the pancreas

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Abstract. – Intraductal Papillary Mucinous Neoplasms (IPMNs) are the most common cystic tumors of the pancreas and are considered premalignant lesions. IPMNs are characterized by the papillary growth of the ductal epithelium with rich mucin production, which is responsible for cystic segmental or diffuse dilatation of the main pancreatic duct (MPD) and/or its branches. According to the different involvement of pancreatic duct system, IPMNs are divided into main duct type (MD-IPMN), branch duct type (BD-IPMN), and mixed type (MT-IPMN). IPMNs may be incidentally discovered in asymptomatic patients, particularly in those with BD-IPMNs, when imaging studies are performed for unrelated indications. The increase in their frequency may reflect the combined effects of new diagnostic techniques, the improvement of radiologic exams and progress in the recognition of the pathology. MD-IPMNs present a higher risk of malignant progression than BD-IPMNs; as a consequence, all the guidelines strictly suggest the need of surgery for MD- and MT- IPMNs with MPD > 10 mm, while the management of BD-IPMNs is still controversial and depends on several cysts and patients features. The choice between non-operative and surgical management depends on the distinction between benign and invasive IPMN forms, assessment of malignancy risk, patient's wellness and its preferences.

This manuscript revises the different guidelines for the management of IPMNs that have been published in different world countries: the international (Sendai 2006 and Fukuoka 2012), the 2013 European, the 2014 Italian, and finally the 2015 American guidelines. In summary, this review will integrate the recent insights in the combination of diagnostic techniques, such as Magnetic Resonance Imaging (MRI) and endoscopic ultrasound (EUS), pathology classification, and management of IPMNs.

Key Words:
Pancreatic cyst, Intraductal papillary mucinous neoplasms of the pancreas, MD-IPMN, BD-IPMN, MT-IPMN, FNA, Endoscopic ultrasound.

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) have emerged as the most common mucinous cystic neoplasms of the pancreas, and they represent a significant clinical entity. IPMNs are considered as a premalignant pancreatic lesion that are characterized by the papillary growth of the ductal epithelium with rich mucin production, which is responsible for cystic segmental or diffuse dilatation of the main pancreatic duct (MPD) and/or its branches. These epithelial cells can be of four different histological types: (1) gastric, (2) intestinal, (3) pancreatobiliary, (4) Oncocytic[1]. These cells can exhibit a wide spectrum of dysplasia, from mild- intermediate- and high-grade dysplasia to invasive carcinoma. Invasive carcinoma (papillary mucinous carcinoma, according to last 2010 WHO classification) is considered a malignant tumor and is associated with poor prognosis[2]. IPMN accounts 1-2% of all pancreatic pathologies, 3.2% of all neoplasms of the pancreatic gland, 4.8% of all exocrine pancreatic neoplasms and of 21%-41% of all cystic neoplasms of the pancreas[3]. IPMNs are typically associated with a high secretion of mucin.

According to the involvement of pancreatic ductal system, IPMNs are divided into: main duct type (MD-IPMN), branch duct type (BD-

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IPMN), and mixed type IPMN (MT-IPMN). MD-IPMNs are characterized by segmental or diffuse dilatations of the main pancreatic duct > 5 mm, without other causes of obstruction. Particularly, the diameter of the MPD is normally 3.5 mm in the head, 2.5 mm in the body, and 1.5 mm in the tail[4]. BD-IPMNs are cystic dilatations of the pancreatic duct branches which have to maintain the communication with Wirsung duct. They can be unifocal or multifocal, and they must be distinguished by pseudocysts in people who have a history of pancreatitis. MT-IPMNs are dilatations of both the main pancreatic duct and its branches.

IPMNs frequently affect the head of the pancreas (50%), but also the tail (7%), and the uncinate process (4%), with the remaining (39%) affects throughout the pancreas (multifocal IPMN). Up to 41% of BD-IPMNs are multifocal with more than two lesions. Moreover, IPMNs mainly affect elderly people (age 60-70), with an equal sex distribution[1].

The first case of IPMN was described by Ohashi et al[5] in 1980 who reported in one of their patients the presence of an invasive pancreatic cystic lesion with profuse mucin secretion, which formed a fistula draining into the common bile duct. Since then, a large number of similar cases have been described. The increase of IPMNs frequency may reflect the combined effects of new diagnostic techniques, the improvement of radiologic exams and progress in the recognition of the pathology.

Clinical Presentation

Usually, IPMNs are not related to a typical clinical pathognomonic presentation. In particular, BD-IPMNs associated symptoms are vague and often non-specific. In a large amount of cases, BD-IPMNs may be incidentally discovered in asymptomatic patients, when imaging studies are performed for unrelated indications[6]. On the contrary, in patients with MD-IPMNs, the obstruction of the MPD system may cause abdominal pain, due to the mucin hyperproduction which obstructs normal pancreatic secretion, and/or single or recurrent episodes of acute pancreatitis from mild to moderate severity. Other associated symptoms may be: abdominal pain (50-70%), followed by weight loss (20-40%), nausea and vomiting (11-21%), jaundice (15-20%), acute pancreatitis (15%), back pain (10%), that are related to the stage of the disease (Table I). In the case of voluminous cysts, patients may stop eating to avoid pain, while in degenerated malignant cysts, anorexia may be related to neoplastic factors. The onset of diabetes may be related to the chronic occlusion of the Wirsung duct with viscid mucin that determines endocrine pancreatic insufficiency[7]. Furthermore, some patients may have persistent hyperamylasemia for many years, due to exocrine pancreatic insufficiency, and jaundice, which is a consequence of obstruction of the common bile duct by mucin, mural nodules or by its direct compression by the size of IPMN. Infrequently, IPMNs can fistulate into the stomach, duodenum, choledochus, pleura, colon and small intestine[8]. Fistulization is a severe rare consequence of the chronical persistence of the IPMN. It may be related to several mechanisms that include both mechanical penetration due to the excessive pressure of the mucin in the pancreatic ducts, and inflammation or autodigestion by the pancreatic enzymes highly present in the ducts. Then, fistulization may be the consequence of the direct invasion of the malignancy, in the case of invasive IPMNs[9].

Moreover, it is important to underline that an association of IPMNs and extra-pancreatic diseases has been observed: familial adenomatous polyposis (FAP), familial BRCA2-mutated breast cancer, Peutz-Jeghers, thyroid tumor, colon-rectal cancer, Von Hippel-Lindau (VHL) syndrome, familiar pancreatic cancer, and also an association with autoimmune disease[10,11].

Histological Aspects

Overall, IPMNs are rare tumors of the pancreas but they have a good prognosis if they are discovered in the initial stage. IPMNs may be followed during the time and they can be treated with surgery before they begin to degenerate. IPMNs present a wide heterogeneity degree

Table I. Clinical manifestations of IPMNs.

Clinical symptoms	%
Epigastric discomfort	50-70
Weight loss	20-40
Jaundice	15-20
Back pain	10
Nausea and vomiting	11-21
Acute pancreatitis	15
Diabetes, anorexia, hyperamylasemia,	< 5

of dysplasia and their natural history may be compared to adenomas of the colon. The risk of harboring malignancy is high when IPMNs present features of degeneration, such as containing invasive carcinoma areas, mural nodules, intra-cystic septa, thickened and enhancing cystic walls, and enlargement of Wirsung caliber[12]. MD-IPMNs are associated with higher risk of malignant transformation and more rapid growth, compared with BD-IPMNs, which are commonly considered a more indolent disease. The reported case series of IPMN patients have revealed that the mean frequency of malignancy for MD-IPMNs is about 60%, while for BD-IPMNs is about 25%[1].

The first classification of the mucinous neoplasms of the pancreas, which included both intraductal papillary mucinous tumor and mucinous cystic tumor, was made in 1996 by World Health Organization (WHO)[13]. Then, in 2000, the two neoplasms were renamed as intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), respectively[14]. Later, IPMNs were named and classified in: A. benign (intraductal papillary mucinous adenoma); B. borderline (intraductal papillary mucinous tumors with moderate dysplasia); C. malignant (intraductal papillary mucinous carcinoma, noninvasive or invasive)[15]. Finally, the current pathological classification subdivides IPMNs in: low-, moderate-, and high- grade of dysplasia, and finally invasive carcinoma[1,16].

IPMN cells can be associated with four subtypes of papillary epithelial cells: gastric, intestinal, pancreatobiliary, and oncocytic. Then, there are three histological variants of invasive carcinoma: 1. IPMN-tubular carcinoma, that is usually associated to gastric and pancreatobiliary type; 2. IPMN-colloid carcinoma, which is usually associated to intestinal type; 3. IPMN-oncocytic carcinoma that is usually associated to oncocytic type[1]. These histological variants have different prognostic implications[17,18]. The prevalence of the intestinal type is 18-36% in MD-IPMNs, gastric type is 49-63% in BD-IPMNs, pancreatobiliary type is 7-18% of all IPMNs, and oncocytic type is 1-8% of all IPMNs[7]. Oncocytic and colloid type are associated to a better outcome than tubular type[16]. The invasive carcinoma that arises from intestinal-type IPMNs is often colloid, which has a more indolent behavior[7,17,19]. The gastric type has a worse prognosis than intestinal type, even if only a small percentage of it, developing into carcinoma[9].

The current staging classification of IPMN-invasive carcinoma (tubular, colloid and oncocytic) by the 2010 "American Joint Committee on Cancer/TNM Classification of Malignant Tumors (AJCC/TNM)"[20] proposed a sub-staging of T1 stage in: T1a for those that are ≤ 5 mm, T1b for those that are > 5 mm and ≤ 10 mm, T1c for those that are 10-20 mm.

Another histochemical aspect of interest of IPMNs is the study of the mucins pattern. Intestinal type usually shows diffuse expression of mucin 2 (MUC2), gastric type usually expresses mucin 5AC (MUC5AC) but is mucin 1 (MUC1)-negative, the pancreatobiliary and oncocytic type usually expresses MUC5A and MUC1[21]. Mucin patterns have been studied in a cellular line ASAN-PaCa, derived from an invasive pancreatic adenocarcinoma of a 62-years-old female, with a story of pancreatobiliary type-IPMN[22]. In particular, MUC1 is associated to neoplastic proliferation, progression to malignancy, and invasive phenotype[23].

Moreover, recent data demonstrated that the quantitative histopathology may be an efficient way to distinguish malignant pancreatic carcinoma from MD- or BD-IPMNs, even in a contest of chronic pancreatitis. Quantitative histopathology is approximately 90% accurate in classifying pancreatic lesions and 100% accurate in identifying chronic pancreatitis[24]. In the case of lesions without clear invasion, the quantitative histopathology permit to analyze nuclear features on biopsy specimen (such as nuclear roundness, run length matrix, short run emphasis, long run emphasis, run percentage, total number of lightly stained pixels), and combined with statistical analysis, it is able to distinguish the different entities[24]. Thus, quantitative histopathology is a new technique useful in assisting pathologists in the risk-stratifying of patients with ambiguous pathology.

Finally, the macroscopic morphology of IPMNs is also useful for a better classification and its consequent risk stratification. The morphological pattern of duct dilatation depends on both the tumor location and the mucus production. The following four patterns have been recognized: I. Diffuse MD ectasia; II. Segmental MD ectasia; III. Side branch ectasia; IV. Multifocal cysts with pancreatic duct communication. Each pattern presents specific clinical implications, different prevalence of cancer and therefore, different indications of resection. The presence of multifocal BD-IPMN does not seem to be associated with

an increased risk of malignancy. The reported incidence of malignancy could vary from 57% to 92% in MD-IPMNs and from 6% to 46% in BD-IPMNs[25]. BD-IPMNs are considered premalignant lesions, and their malignant transformation risk can vary based on the size and associated morphological features, such as nodules, multiplicity, and epithelial subtype.

Literature data reported that the mean frequency of malignancy (defined as high-grade dysplasia and invasive cancer) for surgically resected BD-IPMNs is 25.5% (range 6.3%-46.5%), and the mean part that becomes invasive is 17.7% (range 1.4%-36.7%)[1,7,12]. Moreover, in surveillance studies of BD-IPMN patients, the global risk of developing cancer has been reported to be as about 20% during a 10-year period (about 2% per year)[6]. On the other hand, MD-IPMNs and MT-IPMNs have been reportedly associated with a malignancy risk of between 40-92%[12,26,27]. The exact rate of cell transition from benign to malignant is not clear, although the progression of the invasive disease in MD-IPMNs has been estimated to range from 5 to 7 years[1].

Considering the overall prognosis, invasive carcinoma harboring from IPMNs presents a better prognosis than conventional solid ductal adenocarcinoma. The literature data reported that the invasive carcinoma derived from IPMNs has an overall 5-year survival of 34.5% versus 12.4% of primitive ductal adenocarcinoma[28].

Diagnostic Work-up in IPMNs

The diagnosis of IPMNs can be provided thought multiple modalities, such as non-invasive imaging evaluation (MRI/CT), non-invasive endoscopic ultrasound (EUS), and finally invasive ultrasound with fine needle aspiration (EUS-FNA) and fine needle biopsy (EUS-FNB). All these modalities are able to help the clinician to get the morphological features of the cystic lesion, predict or evaluate the presence of malignancy, and stage the disease. Molecular analysis of cystic fluid may provide further important information to distinguish the different pancreatic cystic lesions.

Imaging Evaluation of IPMNs

IPMNs can be suspected on the basis of the aspecific clinical picture or, more often, as an occasional finding during an ultrasound (US) examination, Computed Tomography (CT) scan, or Magnetic Resonance Imaging (MRI) performed for other reasons. These techniques can provide diagnostic features, evidence of malignancy, and staging information.

IPMNs usually appear as cystic formations of small-medium size, hardly detectable on US examination as anechoic lesion. Otherwise, CT scan may be the first examination to reveal these lesions, which appear as clusters of cystic lesions.

CT scan can evaluate macroscopic features, as size of cysts and its anatomical location (head, body, tail; segmental/diffuse), dilatation of MPD, absence or presence of thickened/enhanced walls or mural nodes, lymphadenopathy, pancreatic atrophy[1]. Considering the US or CT scan, the communication between the cystic lesion and the MPD is often difficult to assess. On the other hand, both CT scan may be useful to detect associated signs of chronic pancreatitis (calcifications, ductal stenosis, MPD alterations), malignant degeneration in cases of lesions of major dimensions, altered morphology, solid components or nodules (Figure 1).

In summary, US or CT scan are the first imaging techniques to make the diagnostic suspect of IPMN. However, they aren't the best choice to get the definite diagnosis of IPMN. For this reason, when a cystic lesion is shown by the US and CT scan, other high-resolution imaging techniques are needed to confirm the diagnosis, such as MRI and EUS.

Magnetic Resonance Cholangio-Pancreatography/Magnetic Resonance Imaging (MRCP/MRI) is the most important radiological examination for the assessment of IPMN, both for its non-invasiveness and high sensibility. In particular, MRCP gives information about Wirsung dilatation (segmental or diffuse) and allows showing the communication between pancreatic cysts with the ductal system. International guidelines consider the MPD size between 5-9 mm as suggestive of MD-IPMN ("worrisome features"), and MPD size > 10 mm is considered highly suggestive of malignancy MD-IPMN ("high-risk stigmata")[1].

MRCP/MRI has a high morphological definition due to T2-weighted sequences, that are sensitive to signal coming from static fluid (such as bile and pancreatic juices). CPRM utilizes a long echo time (TE) more than 3000 ms and it allows cholangiopancreatography study to highlight the widespread or segmental dilatation of MPD (typical of MD forms), secondary ducts (BD forms) or both (Mixed forms), with a particular view of

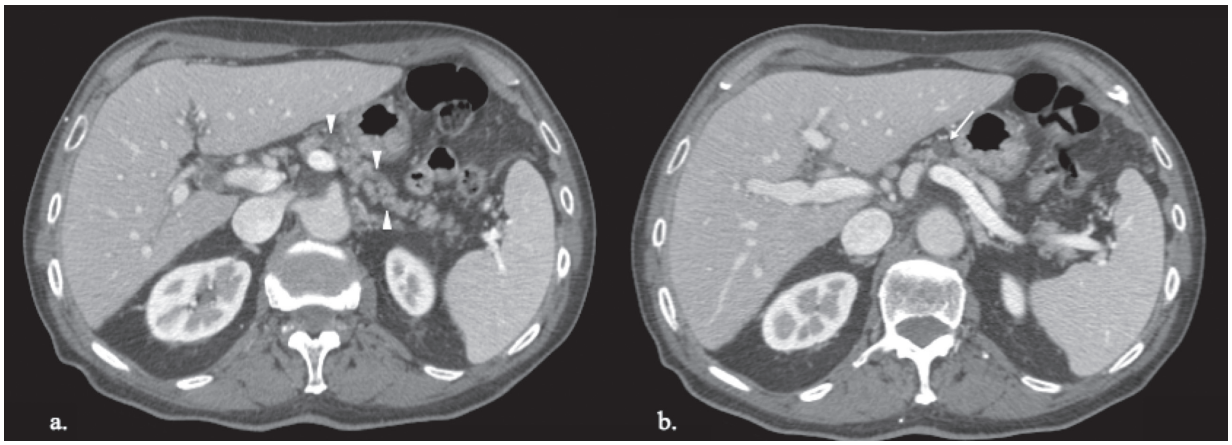

Figure 1. Contrast enhanced CT showing BD-IPMN. ***(a)*** Contrast-enhanced CT shows multiple hypodense structures along the pancreatic isthmus and body, corresponding to dilated secondary ducts (BD-IPMN; white arrowheads), ***(b)*** the largest one of 9 mm in diameter (*white arrow*). The main pancreatic duct is not dilated.

their morphology and communication between cystic lesions and ductal system (Figure 2). MRI can assess altered morphology, solid components or nodules of IPMN by intravenous paramagnetic/iodine contrast medium and T1-weighted sequences (Figure 3). Additionally, MRCP with the use of intravenous secretin may be useful in the better visualization of the complete extent of MPD and secondary branches involvement, and also the definite communication between cysts and pancreatic duct system[29-31]. Moreover, EUS is the second level imaging technique utilized in confirming the suspect of IPMNs. EUS gives integrated and complementary information with MRI. Usually, EUS is performed after that US or CT scan show a cystic lesion. Otherwise, EUS may be performed after MRI to enforce the diagnostic capacity regarding the morphological and anatomical features of the lesion. EUS, as well as MRI, has a high capacity to show anatomical details of cystic lesions and their connections with surrounding structures. In particular, this technique is able to show MPD and its branches course and the multiplicity and obscure communications between ducts. Moreover, EUS can demonstrate morphological features suggestive of malignancy such as mural nodules, irregularity and/or thickening of septa between cysts, and the presence of vessels in these structures[32] (Figure 4). A recent prospective study performed on IPMN patients revealed that EUS and MRCP were equivalent at detecting pancreatic cyst - MPD communications[33]. EUS also allows to perform fine needle aspiration

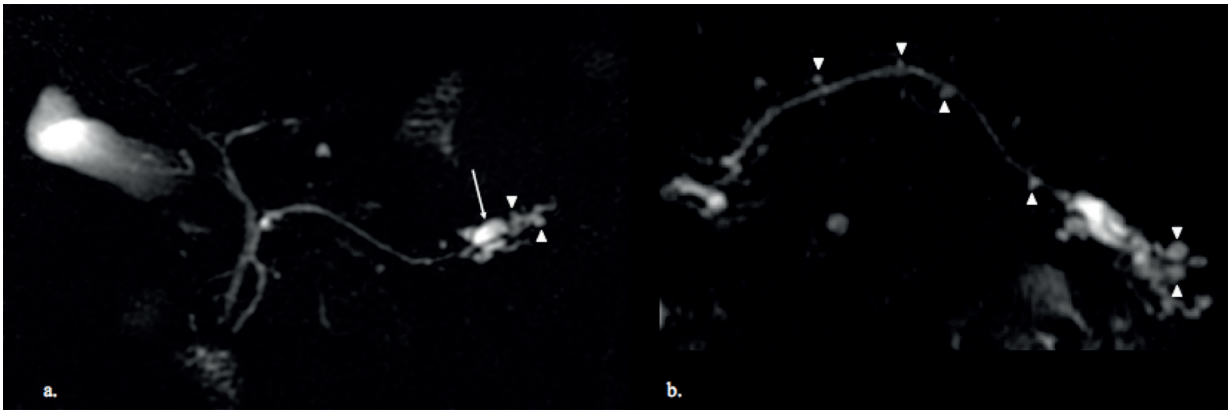

Figure 2. MRCP showing MT-IPMN. MRCP acquired in ***(a)*** coronal and ***(b)*** axial orientation along the axis of the main pancreatic duct shows segmental dilatation of the main pancreatic duct (*white arrow*) and multiple cystic dilated side branch ducts (*white arrowheads*), corresponding to mixed type IPMN (MT-IPMN).

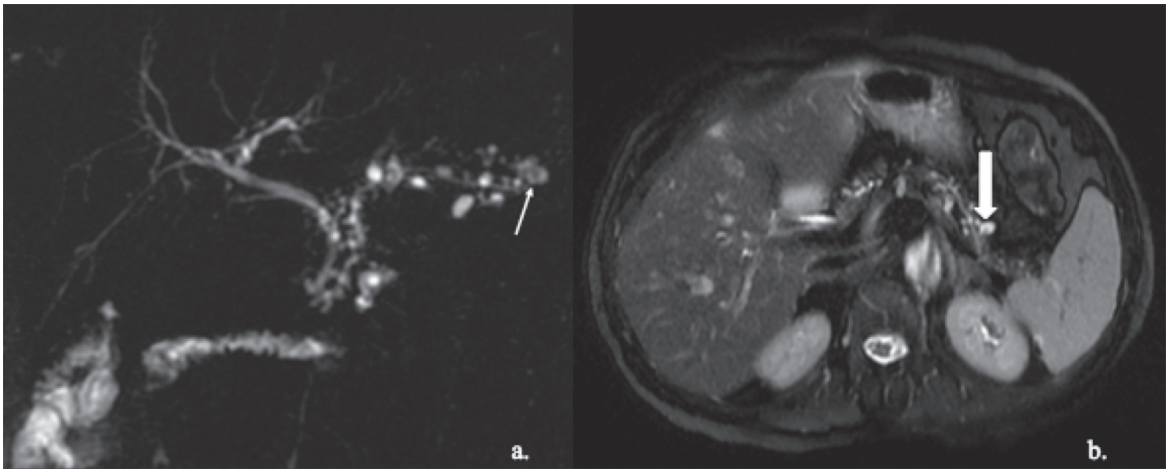

Figure 3. MRCP showing IPMN with worrisome features (*mural node*). ***(a)*** MRCP shows multiple dilated secondary ducts (BD-IPMN); a small filling defect can be found in a cist in the pancreatic tail *(white arrow*). ***(b)*** Axial T2-weighted fat-saturated image (*white thick arrow*) shows a hypointense millimetric mural nodule in the dilated secondary duct in the tail of the pancreas, too small to be detected on post-contrast images. In this case, a close follow-up is required, due to the risk of malignant degeneration.

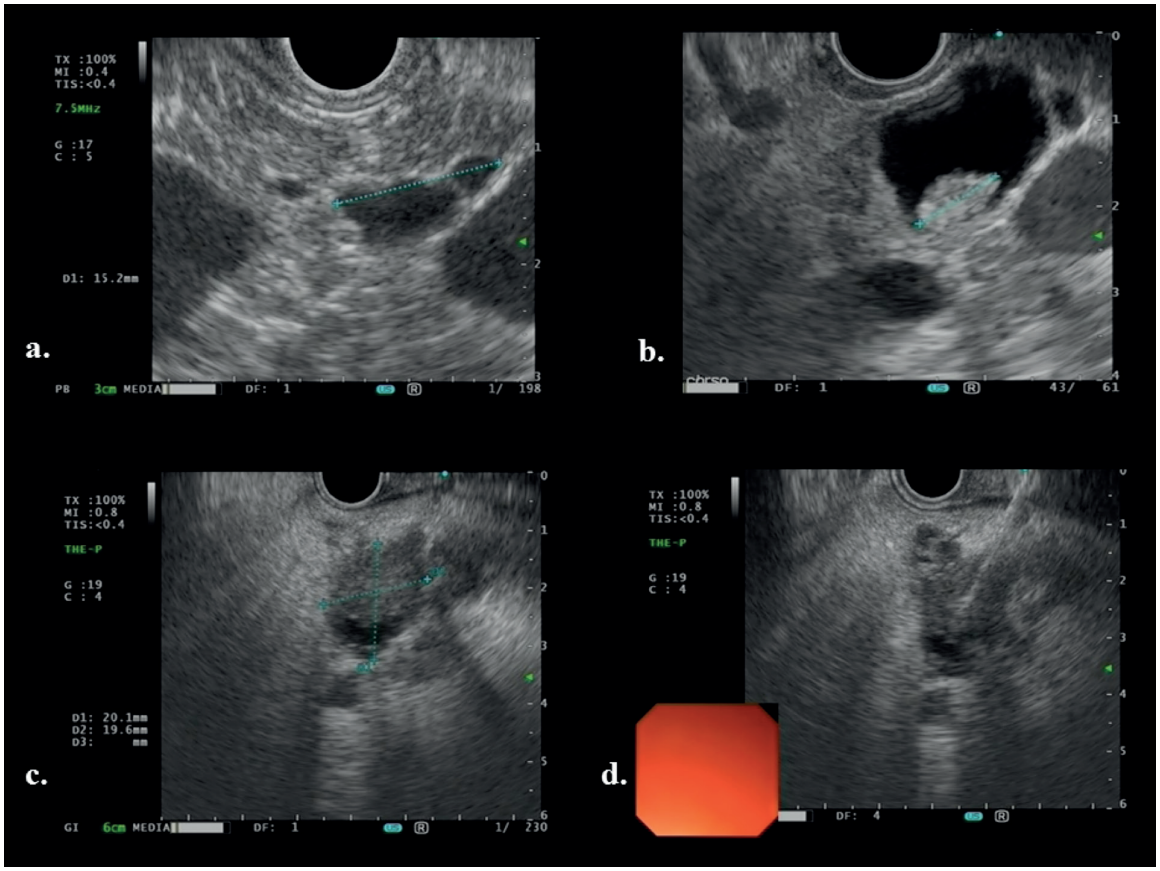

Figure 4. The role of endoscopic ultrasound (EUS) in the assessment and management of IPMNs. ***(a)*** EUS showing a 15 mm BD-IPMN of the pancreatic head constituted by two separated cysts; the confirm of the cyst-pancreatic ductal system communication is achieved through dynamic scansions. ***(b)*** EUS showing a BD-IPMN with a solid intra-cystic component that may be considered as a mural nodule. ***(c)*** EUS showing a papillary mucinous carcinoma deriving from a degenerated BD-IPMN; the picture shows a superior solid component with irregular margins and invasiveness features, and an inferior cystic component that constitutes the initial degenerated cyst. ***(d)*** EUS-Fine Needle Biopsy (EUS-FNB) of the solid component of the same lesion shown in ***(c)*** to perform histological analysis.

(FNA) to analyze the cystic fluid for biochemical or cytological evaluation, which is commonly used for the diagnosis of pancreatic cystic lesions. EUS is easily able to detect malignant changes of IPMNs. In fact, as said before in this review, the use of EUS is recommended in the 2012 FUKUOKA guidelines for management of IPMNs, that even consider this technique more sensitive than CT scan or MRI.

In summary, to evaluate the progression risk in invasive tumor, experts have proposed several clinical and radiological characteristics to classify IPMNs. In particular, these characteristics were reviewed in the 2006 SENDAI consensus conference and then in the 2012 FUKUOKA consensus conference. According to the 2006 SENDAI consensus conference, 'high-risk stigmata' for IPMNs were: presence of mural nodules, MPD > 6 mm, symptoms, positive cytology, and cyst size > 3 cm[34,35]. Then, the 2012 FUKUOKA consensus conference identified high-risk stigmata for IPMN that included enhanced solid component and MPD size of ≥10 mm, and worrisome features that included cyst of ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5-9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and adjacent lymphadenopathy[1,34].

Moreover, when MRI and EUS are not available or contraindicated (for example, patients with pacemaker or claustrophobia, elderly patients, or patients with multiple comorbidities), CT scan may be considered as an alternative choice.

Moreover, it is still debated the role of ^{18}F-Fludeoxyglucose Positron Emission Tomography scan (^{18}FDG-PET-CT) in the radiological assessment of IPMN patients. Literature data revealed that ^{18}FDG PET-CT may be useful for differentiating between benign and invasive IPMNs with high-risk stigmata[9,36,37]. However, PET-CT is not commonly used in the diagnosis and management of IPMN patients.

Endoscopic Retrograde Cholangiopancreatography (ERCP) can be used in the diagnosis and management of IPMNs. ERCP has the dual power to provide further information about pancreatic ductal anatomy and the analysis of the pancreatic juice, when the presence of mucus is suspected. First of all, ERCP may guide the diagnosis of IPMN showing the papilla of Vater features with the side-viewing endoscope. In case of IPMN, duodenoscopy can show a swollen papilla with mucous secretion, that is called 'fish-eye appearance'. Likewise, ERCP is able to facilitate the diagnosis of uncertain pancreatic cystic lesions utilizing invasive techniques, such as pancreatic sphincterotomy. In case of segmental MPD dilatation of unknown origin, the mucin extruding from the papilla after pancreatic sphincterotomy is suggestive of the diagnosis of IPMN. Moreover, ERCP may have therapeutic role in IPMN patients. Endoscopic pancreatic sphincterotomy may be performed in case of recurrent acute pancreatitis episodes due to mucus-related MPD obstruction (Figure 5) but only in patients not candidates for surgery[1]. However, considering its invasiveness, ERCP has been clearly replaced by MRCP as the initial investigation, and it is used only in those patients with uncertain diagnosis.

Additionally, another diagnostic technique under evaluation is per-oral pancreatoscopy (POP). Only few centers can perform POP. Its use is restricted to differentiate between benign lesions of different etiology, such as chronic pancreatitis, from premalignant IPMN lesions[9,38]. The risk of pancreatitis related to POP is the main limitation of the technique.

Biochemical, Molecular and Histological Aspects of IPMN

Blood Tests

To date, there are not any serum pathological markers to predict the presence of IPMNs, and there are not any markers for screening and follow-up of this disease. IPMNs didn't usually cause any significant increase in serum amylase and lipase levels. However, high-size IPMNs may determine an increase in amylase, lipase and/or

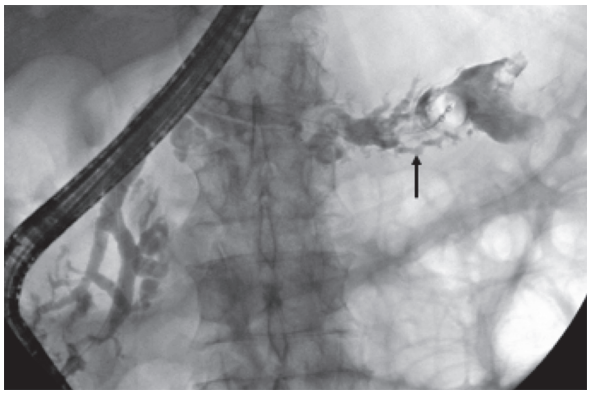

Figure 5. ERCP showing Main Duct-IPMN (MD-IPMN). Mucus presenting as a filling defect (*arrow*) is extracted with a Fogarty balloon during ERCP.

cholestatic enzymes levels in case of compression of the main pancreatic duct and/or common biliary duct.

Serum CA19.9 is not routinely used in the initial biochemical diagnosis of IPMNs, but it has a higher value in the follow-up of IPMN patients. Fritz et al[26] demonstrated that an increase in serum CA19.9 levels may be useful for distinguishing between invasive and benign IPMNs. However, dosing serum CA19.9 is not contemplated in the 2012 International FUKUOKA guidelines for initial diagnosis and management of IPMNs[1]. Whereas, in 2013 European expert's consensus statement, increased serum level of CA19.9 is considered as a relative risk factor predicting malignancy of IPMN patients[36]. Thus, according to these current guidelines, during follow-up, an increase in serum CA19.9 level may be a relative indication for surgical resection of IPMNs[39].

Finally, an anecdotic study reported that other laboratoristic markers may be used to predict invasive malignancy of IPMN, such as neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). The latter are inflammatory markers that are shown to be increased in patients with IPMN related invasive carcinoma[40]. However, NLR and PLR are not utilized in the normal biochemical diagnosis of IPMN patients, and their role may be confirmed in further prospective studies.

Biochemical Analysis of Cystic Fluid After EUS-FNA

EUS is a high-resolution diagnostic imaging of the pancreas that may be utilized in initial management and follow-up of IPMN patients. In particular, EUS may provide information about morphological features of IPMNs and, at the same time, it may be the guide to perform invasive biochemical tests of the cystic fluid after fine needle aspiration (EUS-FNA), and to obtain cystic lesion tissue for histological analysis after fine needle biopsy (EUS-FNB).

Dosing the levels of CEA in the cystic fluid is useful to guide the clinician to differentiate between mucinous cysts (IPMN and mucinous cystadenoma) from non-mucinous cysts (serous cystadenoma and pseudocyst). In particular, the Prospective Pancreatic Cyst Cooperative Study reported that cystic CEA level cut-off should be 192 ng/mL[41]. This level resulted to have a diagnostic accuracy of about 80% (specificity of 84% and a sensitivity of 75%) in revealing the presence of mucinous lesions[41,42].

Notably, if CEA level is $\geq$ 800 ng/mL, the specificity becomes 98%, but sensitivity is only 48%[42]. On the other hand, CEA level in the pancreatic fluid does not correlate with the risk of malignancy. In fact, a previous prospective study[37] reported that even extremely high levels of CEA (> 6000 ng/mL) in the pancreatic fluid of invasive IPMN did not result as a better predictor of the developing of pancreatic cancer. Thus, cystic CEA levels have mainly diagnostic value rather than prognostic one. However, in a very recent data analyzing 286 surgical resected IPMN patients[43], it has been shown that cystic fluid CEA levels are strongly associated with the presence of IPMN-related invasive carcinoma in the cohort of MD- and MT- IPMN patients.

Another cystic fluid marker of IPMNs is amylase level. IPMNs are typically characterized by highly variable amylase levels in the pancreatic fluid due to the connection between cysts and pancreatic duct system[42].

To date, the dosage of CEA and amylase in the cystic fluid after EUS-FNA is the most cost-effective test to determine the mucinous nature of a pancreatic cyst.

Molecular Analysis of Cystic Fluid After EUS-FNA

Literature data[44] demonstrated that molecular analysis of pancreatic cystic fluid may give some other important information for clarify the cyst nature (diagnostic value) and even to predict the evolution to invasive carcinoma (prognostic value).

Several evidences reported that an analysis of a specific panel of several oncogenes and tumor suppressor genes may be useful in the classification and management of pancreatic cysts. In particular, the most common used marker is KRAS. KRAS mutation is considered to be a key event in the development of IPMN, including inactivation of suppressor cyclin-dependent kinase inhibitor 2A (p16) and tumor protein p53 (p53) genes, or the gene products. KRAS is frequently expressed in oncocytic type that it has better outcomes than pancreatobiliary type (which expresses inactivation on p16 and TP53)[45]. Thus, studying KRAS, p53, and p16 (CDK2A) mutations may be useful to differentiate between cancer and chronic inflammatory process.

A large molecular analysis using the next-generation sequencing (NGS) technique demonstrated that the detection of the mutation of KRAS and GNAS is able to reveal the presence of mucinous fluid[45,46]. GNAS and/or KRAS mutations

were found in 92% of IPMN[47]. However, KRAS is also detected in pancreatic juice of chronic pancreatitis patients[48]. For this reason, KRAS is considered to have a low specificity in differentiating between benign and invasive pancreatic lesions. Although the presence of KRAS and GNAS mutations increases in areas of higher degrees of dysplasia, these markers can be present in all grades of dysplasia. Thus, the detection of mutations in KRAS and GNAS is not sufficient to distinguish between benign and invasive IPMN forms[44,47]. Importantly, a very recent literature data have shown the recurrence of single-nucleotide KRAS alterations in pancreatic mucinous cystic neoplasms (MCNs) with high-grade dysplasia. Hence, scholars concluded that the low frequency of KRAS alterations in MCNs without high-grade dysplasia would suggest that they may have a low risk for malignant progression[49]. Then, the oncogene RNF43 can be considered as another marker to confirm the diagnosis of cysts of mucinous type[47].

Furthermore, also the oncogene BRAF appears to be a specific marker of mucinous cysts and its mutations seems to be involved in the progression from benign IPMN to invasive carcinoma[21,48,50]. Finally, the tumor suppressor genes TP53, NOTCH1 and SMAD4 are shown to be involved in the late progression to carcinoma. Their detection can be evaluated using NGS only in specialized centers[47,51].

Other biomarkers helping to classify IPMNs have been individuated, such as IL-8 and IL-1beta in a pancreatic cystic fluid, and T-regulatory cells in peripheral blood[52]. However, to date, there is no evidence of their routinely use in the standard clinical practice.

Additionally, several data have demonstrated that the study of the DNA index may have prognostic value in differentiating between low-grade IPMNs and IPMNs with moderate/high-grade dysplasia. In particular, moderate/high-grade dysplasia is associated with an increase of the DNA index (> 1.3) correlated to the rise of aneuploid cells[53,54].

Finally, the study of Single Nucleotide Polymorphisms (SNPs) has permitted to shown that IPMNs are usually associated with a lower prevalence of SNPs in human chromosomal region 8q24 in respect to the healthy subjects[55].

In summary, the analysis of the panels of specific molecular markers in cystic fluid for detecting IPMNs appears to be an innovative and promising diagnostic technique. To date, it needs to further investigation and confirmatory studies. Then, it is expensive, lacks of standardized analysis method, and is available in only few specialized centers.

Cytological Analysis of Cystic Tissue After EUS-FNA

Cytological analysis of IPMN cystic fluid may reveal the presence of abundant mucin, some inflammatory cells, and even neoplastic cells (either single, cohesive or forming papillae, and mucinous epithelium). The mucin core protein expression of IPMN correlated with the biological behavior and prognosis of the tumor[2]. Immunostaining can demonstrate the cells positivity for MUC1, especially for pancreatobiliary and oncocytic type, which are usually characterized by an high grade of atypia, MUC2, especially for intestinal type, which is characterized by a moderate/high grade of atypia, MUC5AC, especially for gastric, intestinal, pancreatobiliary and oncocytic type, which are characterized by a low grade of atypia, and finally MUC6, especially for oncocytic type, which is characterized by an high grade of atypia[21]. In particular, gastric subtypes demonstrate an overall worse survival outcome when compared to intestinal, pancreatobiliary, and oncocytic subtypes[21,56]. Finally, the tumor suppressor gene VHL, while is a specific marker of serous cystadenoma, is conversely absent in IPMNs.

Histological Analysis of Cystic Tissue After EUS-FNB and EUS-nCLE

Innovation technologies in developing of biopsy needles have permitted to better improve histological analysis of high-risk IPMNs with the presence of solid components, such as mural nodules or thickened walls. So, these novel biopsy needles allow to obtain suspected IPMN solid tissue after EUS-FNB[57].

Moreover, in the last years, a new EUS-guided biopsy system has been developed utilizing a micro-forceps through a 19-gauge (19G) needle that allows to obtain tissue samples from the cystic wall. Moray micro-forceps is a novel and promising techniques that may be used in the determination of the nature of pancreatic cysts and help in their risk stratification and management[58,59].

Finally, the EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) is a novel EUS-guided technique that allows the *in vivo* evaluation of the microscopic features of

the cystic epithelium at the cellular level with a 1,000-fold magnification[60]. However, the use of EUS-nCLE is very expensive and is still an investigational technique.

Management

During the last decade, several guidelines about diagnostic work-up and management of IPMN patients had been published. They analyzed the indication for surgical treatment and postoperative surveillance in patients who have invasive IPMNs, and the follow-up strategies in patients who have a low-risk IPMNs and need a more conservative treatment.

The timing of the follow-up is almost common in all the guidelines, and it is based on the size of the cyst, macroscopic and microscopic features. However, differences and controversies could be appreciated in the choice of the imaging. The three most utilized and validated guidelines developed are the 2006 Tanaka et al[35], 2012 Tanaka et al[35], and 2013 European Consensus Experts[36]. Moreover, other guidelines have been proposed by the Italian Pancreas Group (2014 AISP guidelines)[35], and by the American Gastroenterological Association (2015 AGA guidelines)[61].

The 2006 Sendai guidelines[35] recommended the resection of the majority of BD-IPMNs measuring >3 cm in diameter, even without mural nodules, atypia in the cyst fluid and the presence of symptoms. In contrast, a less aggressive surgical approach has been suggested for asymptomatic, small size (< 3 cm) BD-IPMNs, for which a conservative management was proposed[35]. However, the successive guidelines elaborated over time have gradually suggested a more conservative management for BD-IPMNs.

After the 2006 Sendai consensus meeting, a further experts meeting was taken in 2010 in Fukuoka, Japan, where novel IPMNs management guidelines have been generated and proposed. Thus, the 2012 Fukuoka guidelines included more conservative criteria for the surgical resection of BD-IPMNs. These guidelines presented for the first time the concept of the risk stratification to fit patient undergoing to surgery. In particular, the 2012 Fukuoka guidelines, introduced the terms of 'worrisome feature' and 'high-risk stigmata' (Table II). The 'worrisome features' included cyst size ≥ 3 cm, thickened and enhanced cyst walls, non-enhanced mural nodules, MDP size 5-9 mm, an abrupt change in the MPD caliber with distal pancreatic atrophy, adjacent lymphadenopathy on imaging examinations, and acute clinical pancreatitis[1]. The 'high-risk stigmata' include obstructive jaundice, enhanced solid component, and MPD size ≥ 10 mm[1].

The 2012 Fukuoka guidelines, recommend performing EUS in the case of IPMNs with 'worrisome features'. If EUS is conclusive for definite mural nodules, main duct suspicious for involvement, and cytology suspicious/positive for malignancy, the patients should be undergone to surgical resection. On the opposite, if EUS is inconclusive, close surveillance alternating MRI and EUS every 3-6 months, is recommended. In the presence of IPMNs without 'worrisome features' and suspicious EUS pattern, the guidelines suggest short interval follow-up (3-6 months) to establish the stability, if prior imaging is not

Table II. The 'High-risk stigmata' and 'worrisome features' of IPMNs according to the 2006 Sendai and 2012 Fukuoka guidelines.

	Sendai 2006	Fukuoka 2012
High-risk stigmata	- Presence of mural nodules; - MPD > 6 mm; - Symptomatic presentation; - Positive cytology (cyst size > 3 cm).	- Dilated main duct (≥ 10 mm); - Enhanced mural nodules; - Obstructive jaundice (due to a cystic mass in pancreatic head)
Worrisome features		- Cyst size ≥ 3 cm; - Acute pancreatitis; - Non-enhanced mural nodules; - Thickened, enhanced cystic walls; - MPD 6-9 mm; - Change in duct caliber (MPD stenosis) with distal atrophy; - Adjacent lymphadenopathy.

Abbreviations: MPD = main pancreatic duct.

available. Then, imaging follow-up should be performed according to the size stratification[1]. So, the recommended follow-up according cyst size is: - for cysts < 10 mm, CT/MRI in 2-3 years; - for cysts of 10-20 mm, CT/MRI in 12 months for 2 years, then lengthen interval if no change; - for cysts of 20-30 mm, EUS in 3-6 months, then lengthen interval alternating MRI with EUS as appropriate, and surgery is considered in young, fit patients with need for prolonged surveillance; - for cysts > 30 mm, close surveillance is suggested, alternating MRI and EUS every 3-6 months, and surgery is strongly considered in young, fit patients[1,62]. MT-IPMNs management depends on patient's wellness and lesion biology. Usually, they can be considered for the surgical approach as MD-IPMNs[1]. Finally, the 2012 Fukuoka guidelines suggested that IPMN patients with the presence of 'high-risk stigmata' had to be undergone to surgery resection without delay[1].

In a recent paper analyzing 286 surgical resected IPMN patients[43], it has been shown that among the Fukuoka 'worrisome features' and 'high-risk stigmata', the measurement of cystic associated mural nodules by EUS may be considered an additive important malignant predictor in all IPMN types. Moreover, in a recent retrospective cohort study[63] including 103 MD- and MT-IPMN patients, it has been established that a MPD cut-off of 7.2 mm, instead of the Fukuoka recommended 10 mm, may be better criteria to select a patient to surgery.

In 2013, the European Experts Consensus statement (EECS) differentiated between absolute and relative indications for surgery of high-risk IPMN patients. Absolute indications were based on the 2006 Sendai guidelines, and they showed up the size of the cyst, considering the cut off of 4 cm. Relative indications included the rapid growth speed of the cystic lesion (at least 2 mm/year), and the increased value of serum CA19.9, as marker of malignant progression, even if, as said above in this manuscript, this marker doesn't have a very high validated role in the diagnosis and management of IPMNs[36].

In 2014, AIGO-AISP guidelines reconsidered the Fukuoka definitions of 'high-risk stigmata' and 'worrisome features' giving a different interpretation. These guidelines proposed the indication for surgical treatment for all the pancreatic cysts that, after biochemical analysis by EUS-FNA, revealed a mucinous type, even if they present only the 'worrisome features'. Controversies between the experts working group were about the exact indication for the surgery, and for the imaging to use for the patient's follow-up. However, all the experts agreed for the same follow-up timing and indication of surgery in 'high-risk' IPMN patients[64].

In 2015, the American Gastroenterological Association (AGA) suggested that patients with pancreatic cysts without any Fukuoka criteria or with negative concerning of EUS-FNA should be undergone to an imaging follow-up with MRI in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics. If the cyst remains unaltered after 5 years follow-up, the guidelines suggested stopping the surveillance. On the other hand, pancreatic cysts with the presence of at least 2 Fukuoka criteria, or significant changes in their characteristics should be examined with EUS-FNA. Moreover, these guidelines suggested that patients with a high-risk cyst (such as solid mural nodules, MPD enlargement, and/or high-risk features on EUS-FNA) should be undergone to surgery. Finally, AGA guidelines strongly recommended that high-risk IPMN patients should be referred to selected and specialized Centers for surgery and then the next postoperative follow-up should be with MRI of the remaining pancreas every 2 years[61].

The results of a multicenter IPMNs registry which included 620 IPMN patients have been published. Authors of this study have concluded that among low-risk (Fukuoka negative) BD-IPMN patients the progression rate to malignancy was very minimal and the cysts features during the follow-up remained unchanged[65]. This data may support AGA guidelines idea to limit the follow-up of low-risk IPMNs. AGA guidelines compared to the Japanese and European guidelines seems to utilize a low-intensive follow-up surveillance for pancreatic cysts, seems to make a not precise risk stratification of patients according to the cysts features, and finally they don't routinely consider the use of EUS and its related examinations (such as biochemical and molecular analysis after FNA). For these reasons, in the one hand, AGA guidelines compared to the others allow the reduction of the surveillance costs but, on the other hand, they may present a high risk to not identify and not follow high-risk IPMN patients that may develop malignant progression. Thus, other studies are necessary to better evaluate the best choice for the IPMNs follow-up and surveillance, and they will permit to understand which guidelines will be the best cost-effective (Table III).

Table III. The management and follow-up surveillance of BD-IPMN patients proposed by the different guidelines according to the size stratification.

	Sendai 2006	Fukuoka 2012	EECS 2013	AIGO-AISP* 2014	AGA 2015
< 1 cm	CT/MRI every 12 months.	CT/MRI in 2-3 years	All cysts < 4 cm without **risk factors:**[§] MRI/EUS every 6 months for the year 1, every 12 months for the years 2-5, then every 6 months.[#] If increasing size: 6 months intervals. [§]**Risk factors**: mural nodules, MPD > 6mm. **Relative risk:** increased serum CA19.9 level.	Every 12 months for 2 years, then every 24 months.	MRI in 12 months for the year 1, then MRI every 24 months for 5 years, then stop if no changes.
1-2 cm	CT/MRI every 6-12 months for 2 years, then the follow-up can be lengthened if no change.	CT/MRI yearly for 2 years, then lengthen interval if no change.		Every 6-12 months for 2 years, then every 18 months.	
2-3 cm	CT/MRI every 3-6 months.	EUS in 3-6 months, then lengthen interval alternating MRI with EUS		Every 3-6 months for 2 years, then every 12 months.	
3-4 cm	Resection.	Close surveillance alternating MRI with EUS every 3-6 months.			Cysts > 3 cm should be examined with EUS-FNA and should undergo surgery in case on concerning features.
> 4 cm			Resection.		

*These guidelines are referred to the Italian Association of the Study of the Pancreas. [#]In view of the increasing risk of malignancy related to the age of the lesion. *Abbreviations:* CT, computed tomography; MRI, magnetic resonance imaging; EUS, ecoendoscopy; MPD, main pancreatic duct; BD-IPMN, Branch Duct-Intraductal Papillary Mucinous Neoplasm; EECS, European Experts Consensus statement; AGA, American Gastroenterological association.

The importance of Japanese guidelines has been the standardization of world clinical management of IPMN patients. However, a systematic review of 1,382 surgically resected patients realized by Goh et al[66] has shown that Japanese guidelines present a great sensibility but a lower specificity. For this reason, these guidelines have a low predictive positive value (PPV) considering the evaluation of all type of the pancreatic cysts in general, but they achieve a higher PPV after the stratification of IPMN patients into 'high-risk' and 'worrisome risk' groups. Then, a further study[67] performed on 138 resected IPMN patients have shown that Sendai guidelines would have a better negative predictive value (NPV), while the Fukuoka guidelines seem to have a better PPV.

The surgical treatments of IPMN patients recommended by these guidelines include radical surgical resections, such as pancreaticoduodenectomy or distal pancreatectomy with splenectomy. Pancreatectomy, with lymph node dissection, partly preserving both endocrine and exocrine pancreatic function, is advocated for most patients with IPMNs, while total pancreatectomy may be necessary for some. Otherwise, in these last years, parenchyma-sparing resections, such as central pancreatectomy with splenic preservation or enucleation, have been spreading[1,68].

The result of an important multicenter study[69] of 15-years follow-up of IPMN patients has been published. In this registry of 324 IPMN patients, indications for surgery have been analyzed. In particular, authors have demonstrated that the current consensus guidelines for IPMNs surveillance and surgical indications may not adequately

stratify and identify the patient's risk to harbor invasive IPMN-related cancer. The statistical analysis of this study concluded that, even in the case of the absence of 'high-risk stigmata', each additional 'worrisome feature' may have an additive value in predicting the progression in pancreatic carcinoma. Thus, IPMN patients with multiple 'worrisome features' even in the absence of high-risk factors may be considered appropriate for preventive surgical resection[70].

In the retrospective study by Nagata et al[71], patients with high-risk IPMNs who couldn't be resected for their age, contraindications to general anesthesia, and comorbidities, were periodically followed with imaging, instead of going on surgery. About 46% of the patients with MD-IPMNs developed a pancreatic cancer in 5-year, 19% died for the disease, and 19% for other causes. For BD-IPMNs, the percentage was 4%, 2%, and 6%, respectively. Thus, this study confirmed the well-known fact that MD-IPMNs are associated with a very high-risk of developing pancreatic cancer. Furthermore, this study enforced the importance of the frozen section analysis of the surgical margin to rule out the presence of high-grade dysplasia or invasive cancer[72]. This data suggested and confirmed that IPMNs needs postoperative surveillance based on the resection margin status.

The importance of the frozen section analysis and the next histological examination is further underlined in the 2013 Verona consensus conference. During this conference, experts discussed about the importance to utilize standardized sampling modalities and revised the terminology of IPMNs pathology. Moreover, in the manuscript derived from the Verona conference published in 2016, authors suggested to avoid the term 'minimally invasive', while the study of the microscopic margin is strictly recommended to define better the stage and sub-stage linked with the invasiveness state. Finally, these authors concluded that also the term 'malignant' should not be used and according to the histological microscopic features, the most correct terminology for high-risk IPMNs should be 'invasive'[35,36].

Conclusions

To date, the knowledge of IPMNs pathology is still incomplete, and the understanding of the disease management is evolving. MD-IPMNs and MT-IPMNs present a high risk of malignant degeneration in invasive carcinoma[1]. As a consequence, all the guidelines strictly suggest the need of surgery for MD-IPMNs and MT-IPMNs with a MPD > 10 mm[1,35,36,64]. Compared with MD-IPMNs, the diagnosis, treatment, and surveillance of BD-IPMNs remain still unclear[73].

The aim of the current guidelines and literature data is to perform a precise risk stratification to distinguish between low-risk and high-risk IPMN subtypes, and to fit IPMN patients according to their healthy and comorbidities. The definition of histopathological IPMN subtypes is helpful to get prognostic information. Then, the identification of 'high-risk stigmata' and 'worrisome features' is strongly recommended in order to suggest the best management.

Furthermore, the combination of several molecular markers of pancreatic cystic fluid and clinical, biochemical and imaging information, may improve the classification and risk stratification of pancreatic cysts, and thus, it may correctly guide the management of IPMN patients[74].

In the last decade, the use of EUS has been considerably emphasized in order to its ability to give information on cyst's morphological characteristics, to identify cyst's high-risk features, to become a guide to perform intra-cystic analysis after FNA/FNB, and to manage IPMN patients in the follow-up surveillance. To date, the routine use of EUS is still considered investigational, but EUS-FNA with cytological and molecular analyses may be recommended for evaluation of selected BD-IPMNs even if without 'worrisome features'. However, EUS should be done only in centers with expertise and the presence of a dedicated pathologist.

On balance, clinical patient wellness (age, comorbidities and performance status)[75,76], and the quality of life are likewise important for the correct management of this disease, because each decision to treat or not may be based on the consequent benefits, reasonable and acceptable patient's life. Consequently, the choice between non-operative and surgical management depends on the distinction between benign and invasive IPMN forms, consequent malignancy risk, patient's wellness and its preferences.

Thus, other studies are necessary to better evaluate the best choice for IPMNs follow-up and surveillance, and they will permit to understand which guidelines will be the best cost-effective.

The evaluation and management of IPMN patients require specialized expertise, the profound knowledge of IPMNs pathology with a dedicated pathologist, the use of advanced imaging techniques, such as EUS and MRI with

a dedicated radiologist, and the possibility to perform EUS-FNA with cytological and molecular analyses of cystic fluid. For this reason, in this new era of the modern medicine, IPMN patients should be managed in selected specialized high-volume centers.

As described, although the management of IPMN patients is profoundly based on shared and standardized guidelines, it is important to underline that each case is different from the others, because of the complexity, peculiar clinical and family history, symptoms, comorbidities, perceived pancreatic cancer risk and expectations of each patient.

Finally, we should remember that follow-up and management of IPMNs are also affected by patient compliance, the availability of a precise recall system from the medical staff, and availability of all the diagnostic techniques. For these reasons, IPMN patients should be referred to a dedicated pancreatic team where a multidisciplinary approach is possible.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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