Intraductal papillary mucinous neoplasms and mucinous cystadenomas: current status and recommendations

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ABSTRACT

The real prevalence of pancreatic cystic lesions remains unknown. The malignant potential of some of these lesions remains a cause for significant concern. Thus, it is mandatory to develop a strategy to clearly discriminate those cysts with a potential for malignant transformation from those that do not carry any significant risk. Intraductal papillary mucinous neoplasms and mucinous cystadenomas are mucinous cystic neoplasms with a known malignant potential that have gained greater recognition in recent years. However, despite the numerous studies that have been carried out, their differential diagnosis among other cysts subtypes and their therapeutic approach continue to be a challenge for clinicians. This review contains a critical approach of the current recommendations and management strategies regarding intraductal papillary mucinous neoplasms and mucinous cystadenomas, as well as highlighting the limitations exposed in current guidelines.

Key words: IPMNs. MCAs. Pancreatic cyst. Malignancy.

INTRODUCTION

The term “pancreatic cystic lesion” (PCL) involves a heterogeneous group of pancreatic cysts including totally benign lesions such as pseudocysts and potentially malignant entities such as mucinous cystadenomas (MCAs) or intraductal papillary mucinous neoplasms (IPMNs). Currently, the real prevalence of PCLs remains unknown. Several studies have attempted to elucidate this matter, resulting in a wide spectrum of prevalence estimates ranging from 0.2% to 44.7% (1-4). This wide range is a consequence of significant heterogeneity with regard to the selected population, the type of imaging technique or the subtype of cysts described.

Despite this, there is general agreement regarding an increased trend of incidental PCLs diagnosed in recent years (5,6), mainly due to an aging population and the widespread use of high-resolution imaging technologies (7,8). The malignant potential of some, albeit a small proportion of these lesions, remains a cause for significant concern. Currently, the only accepted treatment is surgical resection, which is an aggressive approach, moreover considering that it may involve benign lesions (9). Thus, it is mandatory to develop a strategy to clearly discriminate those cysts with a potential for malignant transformation from those that do not carry any significant risk.

PCLs include a broad amalgam of cystic lesions including the so-called pancreatic cystic neoplasms (PCNs). There are four main types of PCNs: IPMNs, MCAs, serous cystadenomas and solid pseudopapillary neoplasms (Table I). As its name indicates, these lesions have a potential for malignant transformation (10) that broadly ranges from 1% to 36% (11-14).

Herein, we will focus on the most common mucinous cysts: the IPMNs and the MCAs. Due to their greater recognition (5) and the improved knowledge of their pathway to malignant transformation, these entities have gained increased attention in recent years. However, despite the numerous studies that have been carried out (15), their differential diagnosis among other PCL subtypes and the therapeutic approach continue to be a challenge for clinicians.

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMNs) AND MUCINOUS CYSTADENOMAS (MCAS)

IPMNs

IPMNs were reported for the first time in 1980 (16) and considered as an independent entity since 1996 (17). IPMNs are intraductal lesions characterized by a columnar
Intraductal papillary mucinous neoplasms (IPMNs) are cystic neoplasms of the pancreas characterized by mucin-secreting epithelium that may characteristically present with papillary projections into the pancreatic duct lumen (18). They encompass a spectrum of cystic neoplasms with diverse potential for malignancy, following a progressive pathway of low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to invasive pancreatic ductal adenocarcinoma (19).

IPMNs can derive from the epithelium of the main pancreatic duct (MD) or the side branches (BD) (Fig. 1). This distinction has clinical relevance because MD involvement has been identified as a predictor of malignant transformation (20-23). A MD dilation over 9 mm is considered to be a “high-risk stigmata” whereas a dilation comprised between 5-9 mm is considered as a “worrisome feature” for malignancy (24). There is a third classification named “mixed type IPMN” that comprises both MD and BD involvement. It has been postulated that this category should not be considered as an independent type due to their same clinicopathologic behavior as MD-IPMNs. However, in recent consensus guidelines it remained as a distinct subtype due to its interest from a pathological point of view (24,25). BD-IPMNs, on the other hand, are the main subject of debate nowadays. Initially, the main recommendation was to resect them due to their malignant potential. However, several recent studies have reported significantly lower rates of malignant transformation (ranging from 2-6%) (26-29), which has leaned the balance towards a more conservative approach.

IPMNs are also classified according to the histological subtype, which is associated with anatomic (MD versus BD) location. This classification has clinical importance because it predicts the IPMNs biological behavior (30). Four different subtypes have been described: gastric, intestinal, pancreatobiliary and oncocytic (24). The majority

<table>
<thead>
<tr>
<th>Variables</th>
<th>IPMN</th>
<th>MCA</th>
<th>SCA</th>
<th>SPN</th>
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<tbody>
<tr>
<td>Age</td>
<td>60-70</td>
<td>40-50</td>
<td>50-70</td>
<td>20-40</td>
</tr>
<tr>
<td>Gender</td>
<td>Slightly more prevalent in males (60%)</td>
<td>Females (&gt; 90%)</td>
<td>Females (75%)</td>
<td>Females (&gt; 90%)</td>
</tr>
<tr>
<td>Pancreatic location</td>
<td>Anywhere</td>
<td>Distal (body and tail)</td>
<td>Anywhere</td>
<td>Distal (body and tail)</td>
</tr>
<tr>
<td>MD communication</td>
<td>Present</td>
<td>Typically absent (85%)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Macroscopic appearance</td>
<td>Macrocystic (BD)</td>
<td>Oligocystic or macrocystic</td>
<td>Microcystic (honeycomb pattern)</td>
<td>Macrocystic</td>
</tr>
<tr>
<td>Malignant potential</td>
<td>Low (BD)</td>
<td>Low</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>Predictors of malignancy</td>
<td>High (MD)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Size &gt; 3 cm</td>
<td>Mural nodules</td>
<td>Peripheric calcifications</td>
<td>Big size</td>
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<tr>
<td></td>
<td>MD &gt; 6 mm</td>
<td>Thickened and irregular walls</td>
<td>Irregular walls</td>
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IPMN: Intraductal papillary mucinous neoplasm; MCA: Mucinous cystadenoma; SCA: Serous cystadenoma; SPN: Solid pseudopapillary neoplasm; MD: Main duct; BD: Branch duct.

Fig. 1. Morphological classification of intraductal papillary mucinous neoplasms. Coronal view of several magnetic resonance cholangiopancreatographies showing main duct (A), mixed type (B), and branch duct (C) intraductal papillary mucinous neoplasms.
of MD-IPMNs are the intestinal subtype, which tends to progress to colloid carcinoma and has a better prognosis than conventional adenocarcinoma. On the other hand, BD-IPMNs are usually a gastric subtype that is mainly benign. However, if malignancy develops from this cell lining, it is a tubular carcinoma, which has a poor prognosis similar to pancreatic ductal adenocarcinoma (31).

IPMNs are usually diagnosed incidentally in middle aged and older patients (32) with a slightly higher prevalence in males (60%) (33). They are frequently located in the head of the pancreas but may also have a multifocal presentation throughout the gland (34). In MD-IPMNs the “fish mouth” sign, consisting of mucus extruding through the papilla, is a pathognomonic sign reported in 22 to 55% (35) of the cases. Moreover, the presence of mucus drainage through a pancreaticoduodenal fistula is seen in up to 2% of the cases and is suggestive of underlying malignancy (36).

The biomarkers seen in IPMNs include p16/CDKN2A, SMAD4 and TP53 (37,38). Moreover, the loss of expression of p16/CDKN2, CDKN1C and ppENK may also be observed in these lesions (39). Recently, several studies (40-42) have demonstrated the presence of GNAS (mainly in the intestinal subtype) and/or KRAS (pancreatobiliary subtype) mutations in up to 96% of IPMNs. GNAS mutations have become a promising diagnostic tool, as they seem to be selectively present in IPMNs and, consequently, absent in MCAs. Unfortunately, this GNAS mutation is not seen in every IPMN and, thereby, is still far from being considered as the gold standard for IPMN diagnosis.

Overall, one of the main concerns regarding IPMNs is their uncertain natural history. Initially, the majority of the publications reported surgically resected cohorts leading to an overestimation of their malignant potential secondary to selection bias. Recent studies, based on observational cohorts, have shown noticeable lower risks of malignancy (43). Thus, newer recommendations tend to follow a more conservative approach especially for the BD-IPMNs with no “worrisome features” (44).

MCAs

MCAs are a different type of PCNs that comprises 25% (45) of the resected lesions. The presence of an ovarian type stroma that supports a mucin-secreting columnar epithelium is a pathognomonic sign of this entity.

Although quite low, MCAs have a potential for malignant transformation as well. The inner epithelium of MCAs may present areas with pseudopyloric, gastric, foveolar and small and colonic intestinal differentiation. Taking into consideration the highest grade of cytological atypia, MCAs can be further categorized into LGD, HGD and invasive carcinoma, the latter resembling conventional pancreatic ductal adenocarcinoma (46). If invasive malignant disease arises in these lesions, the prognosis is poor with a reported post-surgical 5-year overall survival as low as 17% (47).

MCAs are predominantly diagnosed in asymptomatic female patients in their 4th-5th decade of life. Macroscopically, they are solitary homogeneous mucocystic lesions presenting in the distal (body and tail) gland that characteristically do not communicate with the pancreatic duct (48). Typically, they have septa and, occasionally, they may also present with calcifications or nodules (13), the latter suggesting malignancy (Fig. 2).

Due to their usual location in the distal (tail) gland (which generally allows a distal pancreatectomy with less secondary effects and comorbidities [49]), the typical presentation in young patients, and their poor prognosis if malignancy develops (47), surgical resection is primarily indicated (24). Despite this, a recent retrospective study evaluated 90 patients with a surgically resected MCA (50). Of these, only 6% were HGD and 4% were harbored invasive carcinoma, concluding that, in the absence of symptoms, MCAs smaller than 3 cm with no mural nodules or elevated tumor markers may not need resection. However, the authors suggested that validation with a prospective study is needed. Even if these results are validated, it seems that a life-long surveillance program for these, generally young patients, may carry significant costs, as well as anxiety for the patient, compared to surgical resection that does not need further follow-up based on current literature findings (51).

Several epithelial markers have been proposed for MCAs, such as carcinoembriogenic antigen (CEA) and...
cytokeratins 7, 8, 18 and 19, as well as the gastric foveolar type markers such as MUC5AC (with MUC1 being present in malignant MCAs). Also, K-ras, p53, RNF43 and SMAD4 mutations may be seen in dysplastic and invasive MCAs (40,52).

MCAs usually have an elevated CEA (53) in cyst fluid that can help to discriminate these lesions from serous cystadenomas (which also tend to present as solitary lesions but have a minimal risk of developing malignancy). However, IPMNs typically have high cyst CEA levels as well. Therefore, it may be difficult to differentiate between these two entities preoperatively (54). Another added challenge is the pancreatic duct communication that theoretically is only patent in IPMNs. Despite this, a study showed that at least 15% of pathologically confirmed MCAs had a communication between the lesion and the MD (13).

Whereas current guidelines recommend resection for all suspected MCAs, clinically suspected IPMNs must undergo further classification to discriminate which lesions should be resected (due to their high risk of developing malignancy) and which should undergo periodic surveillance. Hence, it is mandatory to design a preoperative strategy to categorize and discriminate among IPMNs and MCAs due to their different management and prognosis.

DIAGNOSIS

Presently, the reported agreement between preoperative diagnosis and the pathology for PCLs is comprised between 68-78% (55-57). A combined strategy between the different imaging modalities as well as techniques that allow tissue/fluid sampling, such as endoscopic ultrasound (EUS), is currently recommended, at least for larger or worrisome lesions, to characterize and define these lesions (57,58).

Imaging studies

To date, there have been several studies that have reported the insufficient accuracy of current imaging modalities to discriminate PCLs (59,60). Despite this, magnetic resonance cholangiopancreatography (MRCP) is currently considered to be the best imaging technique for detection and characterization of both IPMNs and MCAs. This modality groups the routine contrast-enhanced magnetic resonance imaging with fast spin-echo sequences, allowing 3D reconstructions of the pancreatic and biliary trees. Overall, this technology has the ability to detect ductal communications as well as the presence of clinically relevant intracystic features such as mural nodules (61).

Recently, a study (62) showed no differences between MRCP and multidetector computed tomography for the characterization of these lesions. The combination of both modalities was not significantly better than each of them alone, however, the authors suggested that both techniques could be used together in selected difficult cases where no clear radiologic pattern is seen.

Even if MRCP and the multidetector computed tomography have the same accuracy, the absence of radiation in the case of MRCP offers more advantages especially in younger patients. Also, MRCP seems to carry lower risk of undesirable effects secondarily to contrast administration (63).

Endoscopic modalities

Recently, the ASGE published new guidelines regarding the role of endoscopy in the diagnosis of PCNs (64). These guidelines aimed to describe the utility of the different endoscopic modalities especially in those cases were no characteristic radiological features of the cysts are seen, and inconclusive information is obtained from the primary examinations.

Endoscopic retrograde cholangiography (ERCP) allows pancreaticography, which may be helpful in the differential diagnosis among IPMNs and MCAs if communications or segmental strictures in the pancreatic duct are seen. However, these findings are not specific for PCNs as they can also be described in pseudocysts or chronic pancreatitis, respectively. One advantage of this technique is that tissue sampling can be performed via brush cytology or random biopsies. Nevertheless, a recent systematic review (65) that analyzed 483 IPMN patients demonstrated that ERCP-based cytology had a good specificity (97%) but an insufficient sensitivity (35%) with an overall accuracy of 93%. In this same review, lavage cytology was the best approach with a sensitivity of 46% and a specificity of 98%. New technologies for tissue sampling such as intrapancreatic videoscope with fiberoptic probes have been tested (66), showing excellent results with 100% sensitivity and specificity for detecting malignancy via irrigation cytology in patients with dilated MDs (67). Despite these promising results, ERCP is rarely indicated for PCN diagnosis due to the inherent risks related to the procedure and the current insufficient diagnostic accuracy.

EUS is currently the preferred endoscopic modality to diagnose, sample and follow-up PCNs. One of the main limitations, however, is the significant variability between observers (68) in the description of morphological findings. This can be implemented with the performance of fine needle aspiration (FNA) targeting cyst fluid, intracytomic components, pancreatic ducts or lymph nodes (69,70). Moreover, it has been reported that the combined use of EUS-FNA with a high-resolution imaging modality can increase the diagnostic accuracy up to 54% (71). On the other hand, differentiation between intracytomic mucus versus mural nodules is usually challenging in EUS. To address this matter, a recent study (72) reported that mural nodules tend to appear with ill-defined borders and
a hyperechoic center, as opposed to mucus that usually presents with a hyperechoic rim and hypoechoic center. Recently, contrast-enhanced EUS has seemed to provide valuable information regarding the vascularity perfusion characteristically seen in mural nodules (73), contributing to the current problematic regarding the differential diagnosis with intracystic mucus. Lastly, several studies have demonstrated an increased efficacy of EUS if combined with through-the-needle confocal laser-induced endomicroscopy. In fact, a recent study (74) showed a diagnostic accuracy of 93% when discriminating mucinous cysts if cystoscopy was also added to this technique. Moreover, the results showed a superior diagnostic accuracy if both techniques were performed combined versus independently (87% laser-induced endomicroscopy and 83% cystoscopy, respectively).

Cyst fluid

Cytology of cyst fluid is usually challenging due to the small fluid specimen in most cysts less than 1-2 cm diameter, insufficient presence of cells and cellular contamination secondary to the path of the needle (such as gastric or duodenal wall cells). Thereby, the sensitivity of cytology in cyst fluid has conventionally been very low. A recent meta-analysis (75) that reviewed 1,438 patients with a PCL reported an insufficient sensitivity of 54% and an optimal specificity of 93% to distinguish mucinous from non-mucinous cysts. To try to overcome the cytology deficiencies, one previously reported strategy was to redefine the concept of a “positive” sample as the presence of sufficient high-grade atypical cells that would not be quantitatively or qualitatively enough for cancer diagnosis (76). With this modified concept, the sensitivity and specificity to predict HGD or invasive carcinoma in mucinous cysts were 72% and 85% respectively. Another group (77) published similar results when an exclusive-IPMN cohort was analyzed with a sensitivity and specificity of 77% and 80%, respectively. Nevertheless, their sensitivity dropped to 67% if only BD-IPMNs of less than 3 cm were included in the sub-analysis.

Secondary to the insufficient accuracy of cytology in cyst fluid, several fluid markers have been tested and continue to be evaluated. The most common one is the CEA. There is general agreement that the usefulness of CEA solely lies in discriminating among mucinous and non-mucinous cysts (78); CEA levels > 800 ng/ml have been reported to carry a positive predictive value up to 94% and an overall diagnosis accuracy of 79% (79). Despite this, there is not a clear consensus regarding the optimal CEA cut-off value (80), with 192 ng/ml being the most commonly used (54) (sensitivity of 75%, specificity of 84%). Also, a recent study (81) evaluated the clinical significance of serial CEA measurements by analyzing 400 patients with PCNs who underwent several EUS-FNAs. In 17 (20%) patients, CEA fluctuations were noticed but these were not accompanied by significant EUS variability. Therefore, CEA level fluctuations do not seem to correlate with clinically significant changes.

Finally, molecular DNA analysis of cyst fluid is currently being developed. Several studies, including the PANDA study involving multiple centers, evaluated the presence of KRAS mutations or allelic imbalance to discriminate among mucinous and non-mucinous cysts, with poor results (82,83). Interestingly, a more recent study (84) has shown the usefulness of molecular analysis, if combined with cyst fluid cytology and CEA, for identifying mucinous cysts (diagnostic accuracy of 73%) versus the use of molecular analysis alone (diagnostic accuracy of 56%). Moreover, another study also showed optimal results of molecular analysis in characterizing malignancy among mucinous cysts (85). Despite these initial results, the role of molecular analysis continues to be confined to specific experimental cases when the conventional approach is inconclusive.

Lastly, GNAS mutations (that can also be studied in pancreatic juice) seem to be the most promising molecular marker after a study that showed its presence in up to 64% of patients with IPMN (83-86). Following these results, GNAS mutations seem to be able to discriminate between IPMNs and MCAs (although their absence does not directly diagnose MCAs, as not all IPMNs express GNAS mutations) but they are not useful to detect malignancy (43). Further research is still needed in this field.

CURRENT GUIDELINES AND RECOMMENDATIONS

The first clinical guidelines for IPMNs and MCAs were published in 2006 (87) with a posterior revision in 2012 (24). These guidelines provided an essential framework for the clinical approach of both IPMNs and MCAs. However, due to the limited clinical data available, they were based on consensus agreement and lack of sufficient scientific evidence to be considered as more than expert recommendations. In fact, a recent systematic review (88) addressed the overall utility of the Sendai guidelines in the management of BD-IPMNs showing an insufficient positive predictive value ranging between 11-52% and a negative predictive value between 70-100%.

Briefly, the 2012 guidelines introduced a two-phase algorithm to predict malignancy in these lesions. It consisted of the presence of “high-risk stigmata” (obstructive jaundice in patients with cysts in the pancreatic head, enhancing intracystic solid component and a dilated MD greater than 10 mm) that straightly directed the patient to surgical resection, and “worrisome features” (cyst size greater than 3 cm, thickened/enhancing cyst walls, dilated MD of 5-9 mm, non-enhancing mural nodules, abrupt pancreatic duct caliber change with distal atrophy and
lymphadenopathy) (Fig. 3), which, if present, should be further studied with EUS-FNA. If none of these features was observed, the clinical management was solely based on the cyst size. Also, these revised guidelines lowered the BD and pancreatic duct dilation threshold to 5 mm to increase the sensitivity of the diagnosis.

Since their publication, multiple studies have evaluated the guidelines accuracy. There seems to be a consensus regarding the higher accuracy of the 2012 guidelines with respect to the 2006 ones (44.8% versus 35.5%, respectively) (89). However, if the risk factors for malignancy are analyzed, the results are quite heterogeneous. Cyst size was the risk factor mostly associated with malignancy in a meta-analysis (90) that included 41 articles (3,304 resected BD-IPMNs) with a reported odds ratio of 62.4, followed by the presence of mural nodules (odds ratio 9.3). Surprisingly, a different meta-analysis (91) that reviewed surgically resected IPMNs concluded that mural nodules was the most associated risk factor for malignancy (diagnostic odds ratio 6.0) followed by MD dilation greater than 5 mm (diagnostic odds ratio 4.4). Based on their results, cyst size was not even related with malignant progression. Similarly, a recent study (92) that also analyzed a BD-IPMN surgical cohort showed the presence of mural nodules and MD dilation as the best predictors of malignancy. Cyst size greater than 3 cm seems to be the most debatable risk factor with some studies (93) supporting its role as an independent predictor of malignancy and other publications (44) recommending a conservative approach with close surveillance if present alone without other “worrisome features”.

In 2015 the AGA published new guidelines for the management of PCNs (94). A significant difference regarding the previous Sendai and Fukuoka guideline was the definition of “malignancy”. In these new guidelines, only studies that reported the presence of invasive adenocarcinoma were considered as malignant and, therefore, included, whereas HGD lesions were not entered in the analysis. Thereby, the AGA guidelines aimed to detect “late neoplasia” instead of incipient malignant lesions as in the 2006 and 2012 guidelines. From a clinical point of view, it seems that targeting “late neoplasia” as the diagnostic threshold may not seem the best approach for the patient due to the high lethality of these lesions once malignancy arises. In view of this, a recent study (95) aimed to assess the accuracy of the AGA guidelines in detecting advanced neoplasia. To do so, 225 patients with a PCL who underwent EUS-FNA were analyzed. Interestingly, they concluded that the AGA guidelines were inaccurate to detect PCLs with advanced neoplasia, reporting a sensitivity of 62%, a specificity of 79%, a positive predictive value of 57% and a negative predictive value of 82%. More importantly, and based on their results, these guidelines were not able to detect 45% of HGD or invasive carcinoma IPMNs.

Also, one of the most controversial points was the recommendation against continued surveillance of these lesions if no high-risk factors (i.e., development of a solid component, increasing size of the pancreatic duct, and/or diameter ≥ 3cm) were noticed after five years of follow-up. Despite the fact that this is the first time that the problematic issue of when to stop surveillance of low-risk lesions was addressed, the poor evidence that is currently available limits its generalizability. Moreover, current literature shows contradictory results regarding this matter, with several studies that analyzed BD-IPMNs reporting the development of malignancy after the initial five year period (28,29,96) whereas other publications showed a trend towards stability once the initial surveillance period has passed (97,98). A recent study involving several institutions analyzed 310 patients with asymptomatic PCLs (99). These patients were followed-up for five years or more resulting in a total of 3 (1%) patients developing malignancy. Patients with 0, 1 or 2 of the previously mentioned high risk factors had a 0%, 1% and 15% of risk of developing cancer, supporting current AGA guidelines recommendations for discontinuation of surveillance in selected low-risk patients. Moreover, a study recently conducted by the Mayo Clinic divided PCLs into Fukuoka positive or negative groups depending on the presence or absence of “high-risk stigmata/worrisome features” respectively (100). These cysts were followed-up...
for a median time of 4.2 years concluding that, among the Fukuoka negative cysts, the 5-year pancreatic cancer risk was 2-3% (0-2% if the malignant cases diagnosed within the six first months of follow-up were excluded). Based on their results, they suggested that surveillance after six months could be done at less frequent intervals than those exposed in the Fukuoka guidelines, supporting the trend exposed in the AGA guidelines towards a more conservative management approach.

CONCLUSIONS

PCNs and, more specifically, IPMNs and MCAs are being increasingly diagnosed in daily practice. Most of these lesions are identified during an imaging study performed for non-pancreatic reasons and, in many cases, that study is unable to provide the necessary information to decide the management approach. Combining a radiologic study with EUS-FNA and serum/tumor markers contributes to characterize and discriminate the lesion. Despite this, there are still false positives that wrongly direct the patient to surgical resection with the corresponding morbidities and secondary effects associated.

Current guidelines lack enough long-term evidence to define a clear management strategy and, thereby, their indications are considered as just expert recommendations. Overall, there is an increased trend towards a more conservative approach of low-risk lesions. Nevertheless, further research is still needed to clearly understand the natural history of PCNs, and more specifically BD-IPMNs.

REFERENCES


