3 Intraductal Papillary Mucinous Tumors Principal and Lateral Branch of IPMT: Preoperative Management, Surgical Indications, and Surgical Techniques

Victoria Alejandra Jiménez-García, Ana Argüelles-Arias, Federico Argüelles-Arias, Rafael Romero-Castro, and Marc Giovannini

3.1 Definition

IPMNs of the pancreas are PCN characterized by adenomatous proliferation of the pancreatic ductal epithelium that may affect the main duct, the branch ducts or both [1] and by neoplastic progression ranging from low-to-high grade dysplasia to invasive carcinoma.

V. A. Jiménez-García (✉) · R. Romero-Castro
Endoscopy Division and Gastroenterology Division, Virgen Macarena University Hospital, Seville, Spain

A. Argüelles-Arias
Radiology Department, Virgen Macarena University Hospital, Seville, Spain

F. Argüelles-Arias
Endoscopy Division and Gastroenterology Division, Virgen Macarena University Hospital, Seville, Spain

Department of Medicine, University of Seville, Seville, Spain
e-mail: farguelles@telefonica.net

M. Giovannini
Paoli-Calmettes Institute, Department of Gastrointestinal Disease, Marseilles, France
e-mail: giovanninim@wanadoo.fr

3.2 Epidemiology

The first cases of IPMNs were reported in 1982 [2]. Their incidence has been increasingly reported [3] after the generalized use of noninvasive cross-sectional imaging procedures such as computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP). These imaging procedures can display incidental pancreatic lesions in up to 45% of patients [4–7] being usually difficult to differentiate between their types [8]. Many incidentally pancreatic cystic lesions could be IPMNs [9]. However, the real incidence of IPMNs remains elusive because many IPMNs are asymptomatic. Probably, IPMNs account for 20–50% of pancreatic cysts and 1–3% of exocrine pancreatic tumors [10–12]. There has been observed an elevated incidence of IPMNs in patients who smoke cigarettes [13], have diabetes [14], Peutz-Jeghers syndrome [15], familial adenomatous polyposis syndrome [16], or a history of familial pancreatic adenocarcinoma [14, 17].

3.3 Classification

IPMNs could be both classified anatomically and histologically.

J. Bellido Luque, A. Nogales Muñoz (eds.), *Recent Innovations in Surgical Procedures of Pancreatic Neoplasms*, https://doi.org/10.1007/978-3-031-21351-9_3

1. *Anatomic classification*. According to the involvement of the pancreatic duct, IPMNs could be classified into three subgroups:
   (a) Main-duct (MD)-IPMNs: The main pancreatic duct is involved and can be diffusely or segmentally dilated without stenosis with intraductal enlargement of mucin-producing ductal cells. Most of MD-IPMNs arise in the pancreatic head and can progress distally with or without affecting the side branches. MD-IPMNs require surveillance due to the risk of progression of the disease and malignancy, observed in up to 50% of MD-IPMNs [18]. Moreover, the entire pancreatic parenchyma has to be displayed during follow-up because of the increased risk of developing new-onset cancer [19, 20].
   (b) Branch-duct (BD)-IMPNs: The branch-side dilated subgroup of IPMNs are usually originated from the uncinate process, although the tail of the pancreas may be also affected. The potential for malignancy in this subgroup is lower, 10–15% [18], although, surveillance is also needed [21].
   (c) Mixed-type (MT)-IPMNs: They present features of the two former subgroups with involvement of both the main and the side branches of the pancreatic duct. Its biological behavior regarding the potential for malignancy is the same as for MD-IPMNs.

   Therefore, the anatomic classification has important practical clinical consequences in assessing the risk for malignancy. In a review of 20 studies including 3568 IPMNs, the risk of invasive carcinoma arising in association with MD-IPMNs was about 44%, while in BD-IPMNs was approximately 17% [22]. However, these figures obtained from surgical series may be higher if compared to radiological series.
2. *Histologic classification*. The epithelial lining of the papillary component of IPMNs can be classified according to morphological characteristics and immunohistochemical reaction against mucin proteins in four distinct histologic subtypes (intestinal, pancreatobiliary, gastric, and oncocytic type), each of them characterized by a different risk for developing dysplasia or malignancy. Invasive carcinomas arising from IPMNs have remarkably important prognostic differences being classified as tubular (ductal), colloid, and oncocyte types.

3.4 Pathogenesis

IPMNs have the potential to develop tumors with different phenotypes. So, these IPMNs present with a wide histological spectrum ranging from low, intermediate, high-grade dysplasia to invasive carcinoma.

The risk of developing malignancy is strongly related to the duct involvement [23]. Thus, a high-risk disease with high-grade dysplasia and invasive carcinoma were found after surgical resection in 61.6% of MD-IPMNs and in 18.5% of BD-IPMNs, respectively [22]. Besides, IPMNs have two peculiar, worrisome characteristics such as the frequent finding of multifocal cystic lesions and the increased risk of developing another cystic tumor or a pancreatic ductal adenocarcinoma (PDA), either synchronously or metachronously [23]. Moreover, malignant progression is not only limited to cystic lesions as flat lesions also have the potential to develop malignancy and they need to be also surveilled [24].

IPMNs follow a classic "adenoma-carcinoma sequence" being estimated the time of progression from low-grade dysplasia to invasive carcinoma around 4–6 years [25]. IPMNs are the second most common exocrine pancreatic tumor after PDA. Otherwise, invasive carcinomas arising from IPMNs have important different morphological and genetic features in comparison to the common PDA [26, 27]. So, there have been found several alterations in oncogenes such as tumor suppressor genes and epigenetic changes in hypermethylation and gene expression.

There are several main molecular features that explain the biological behavior of IPMNs and their complex progression pathways, *KRAS* and *GNAS* somatic mutations the most frequent genetic abnormalities found in IPMNs [28, 29].

Table 3.1 Adapted from Nasca et al. [30]. Rate of mutations in low and high-grade IPMN

Mutations	Low-grade IPMN (%)	High-grade IPMN (%)
KRAS	43–89	31–71
GNAS	41–77	42–72
RNF43	10	25–75
CDKN2A	<5	0–15
TP53	<5	18–20
SMAD4	<5	<5

In Table 3.1, there are expressed the rate of different mutations in low- and high-grade IPMNs according to Nasca et al. [30].

Invasive carcinomas in the pancreas with IPMNs may arise in two ways: in an associated/derived manner or in a distinct/concomitant way [31]. Associated invasive carcinomas may have a poorer prognosis than concomitant ones [32]. Anyway, the pathways of carcinogenesis by which IPMNs may progress to PDA are under study.

These comprehensive histologic and genome profile studies are needed to provide insights into the tumorigenesis of these complex lesions allowing further studies and design strategies to accurately identify both drivers and patients at risk to develop invasive carcinomas and treat them timely and properly.

3.5 Clinical Presentation

Most patients with IPMNs are asymptomatic, especially those with BD-IPMN that have been discovered after cross-sectional imaging modalities were performed for unrelated indications. In surgical series the rate of symptomatic patients is, obviously higher, about 50% in one series, being abdominal pain the most common symptom (41%), followed by weight loss (29%), acute pancreatitis 22%), and jaundice (9%) [26]. Nearly 80% of symptomatic patients have only nonspecific clinical signs such as malaise, nausea, vomiting, abdominal or back pain, or weight loss [33]. Some patients may have pancreatitis-like symptoms or acute pancreatitis attacks. In some cases, exocrine or endocrine pancreatic insufficiency as well as maldigestion may develop.

Patients with IPMNs are at risk for synchronous and metachronous pancreatic carcinoma and extrapancreatic malignancies. Therefore, the symptoms and clinical signs will depend on localization of the tumor. In a surgical series of patients with IPMNs referred for surgery, recent onset of diabetes, diagnosed 5 years before surgery, was found to be associated with a 6.9-fold increased risk of invasive carcinoma [34].

Routine laboratory tests are usually normal. In patients complaint with abdominal pain, there may be elevated levels of amylase or lipase, associated or not with increased levels of bilirubin or cholestasis enzymes. Tumor markers such as carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (Ca 19-9) are elevated in less than 20% of noninvasive cases while if they are elevated are suggestive of malignancy [35]. In a meta-analysis, elevated serum Ca 19-9 had a sensitivity of 52% and a specificity of 88% in detecting malignancy in IPMNs [36]. Elevated serum Ca 19-9 has been included in the revised consensus of Fukuoka guidelines as a worrisome parameter [25]. However, serum elevated Ca 19-9 has not been proved useful in distinguishing high-grade dysplastic lesions and its optimal cut-off has to be determined yet [26].

3.6 Diagnostic Approach

The diagnosis work-up of IPMNs relies on high-resolution cross-sectional imaging and endoscopy techniques and has several goals [37]. Firstly, IPMNs should be differentiated from other pancreatic cystic lesions. Secondly, it has to be determined the type of IPMN. Lastly, malignancy-related findings should be identified.

Radiology To assess accurately the subtype of PCN may be difficult. Gadolinium-MRI and/or MRCP should be the first procedure indicated because it can differentiate around 40–95% of PCN in comparison to 40–81% for multidetector CT scan [21] (Fig. 3.1). So, MRI/MRCP is more sensitive than CT for identifying communication between the cysts and the main pancreatic duct, multiple cysts, nodules, and thickened walls and the size of the main pancreatic duct [21, 25, 38]. MRI also spares patients from ionizing radiation of repeated CT. Nevertheless, multimodal imaging procedures (additional CT, especially dual-phase pancreatic protocol CT) should be performed to assess calcifications, when there is a suspect of malignant PCN or a concomitant pancreatic cancer and to rule out malignant recurrence after surgery for pancreatic cancer. There are radiologic features associated with an increased risk of malignancy in IPMNs: presence of a solid component, an enhanced mural nodule (<5 mm), increasing dilation of the main pancreatic duct, 5–9.9 mm and a large cystic diameter ≥ 4 cm [21].

Endoscopy Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly less employed because of its potential associated risks and the more accurate diagnostic yield and safety profile of endoscopic ultrasound (EUS). At ERCP, a patulous "fish mouth" papilla extruding mucus could be seen with the endoscopic view in advanced cases (patognomonic of MD-IPMN) and brushing cytology and collecting pancreatic juice could be obtained. Anyway, current data do not support the routine use of ERCP [39].

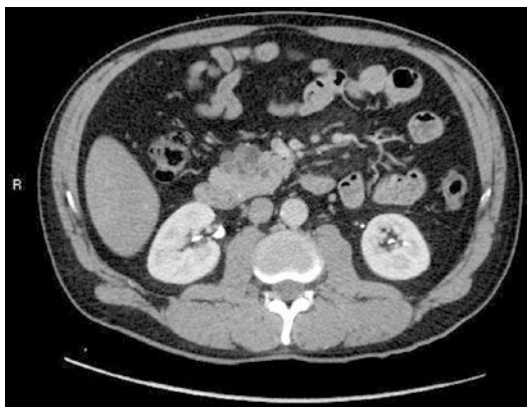

Fig. 3.1 Main duct (MD)-IPMN in the pancreatic head

EUS is the next diagnostic step in the work-up of IPMNs after MRI and CT [25]. EUS provides accurate information on localization, dimensions, and characteristic features such as septation, number of cavities, and calcifications. EUS also assesses mural nodules, the cystic wall, and the entire pancreatic parenchyma to rule out associated solid lesions. EUS has the unique capability to perform EUS-guided fine needle aspiration (EUS-FNA) for solid lesions and cystic lesions to obtain the cystic fluid content for a comprehensive study including amylase/lipase, cytology, proteins antigens, and molecular analyses.

EUS obtains high-resolution images of the entire pancreatic parenchyma and is superior to radiologic techniques, also in assessing mural nodules which are a worrisome feature and one of the stronger predictors of high-risk IPMN. However, mucin plugs could be misdiagnosed as mural nodules. Contrast-enhanced harmonic EUS (CE-EUS) can display the microvascularization of the mural nodules and parenchymal perfusion helping to differentiate them from mucin plugs (Figs. 3.2 and 3.3) with a sensitivity and specificity ranging from 89 to 96% and 64 to 88, respectively [40]. If CE-EUS displays hyperenhancement of a mural nodule, a solid mass, or septations, the concern of malignant transformation is raised and EUS-FNA should be performed according to a European guideline [21]. Besides, to make clinical management of these patients more difficult, not only cystic or mural nodules are worrisome features. Koshita et al. diagnosed with EUS 21 patients with BD-IPMNs with invasive carcinoma. They found 12 patients with mural nodules while 9 patients have flat-type invasive carcinomas with higher recurrence rates of 33 vs. 67% and a worst 5-year survival of 76 vs. 33% in those with flat-type IPMNs [24].

A prospective multicenter study has reported that needle-based confocal laser endomicroscopy (nCLE) performed during the EUS-FNA of a

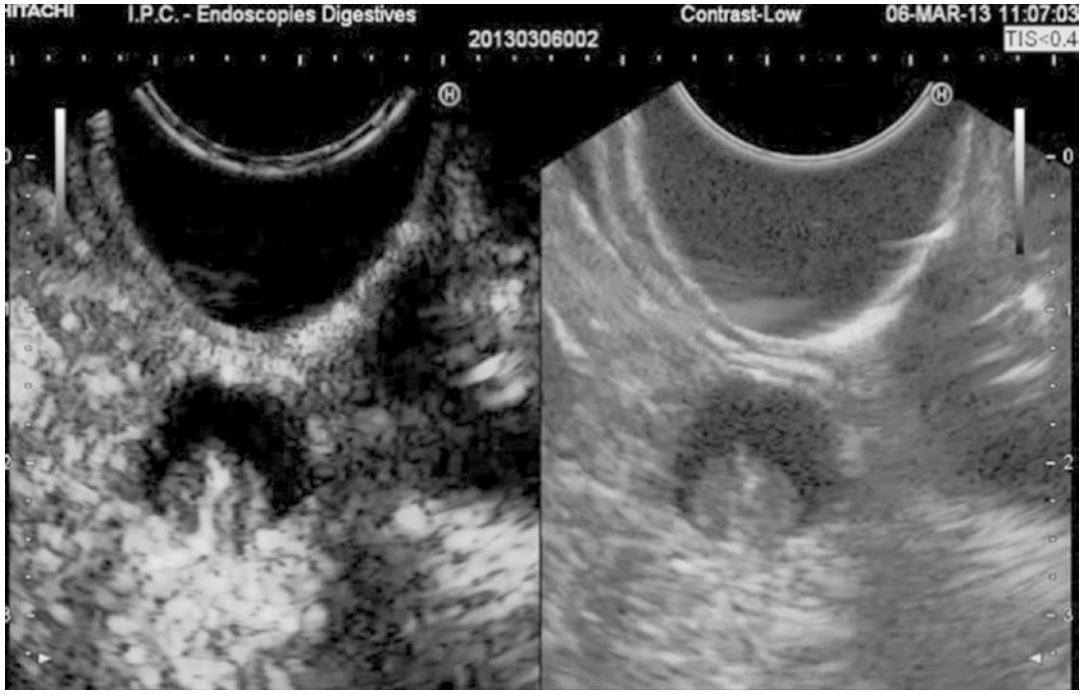

Fig. 3.2 CE-EUS showing the microvascularization of a mural nodule

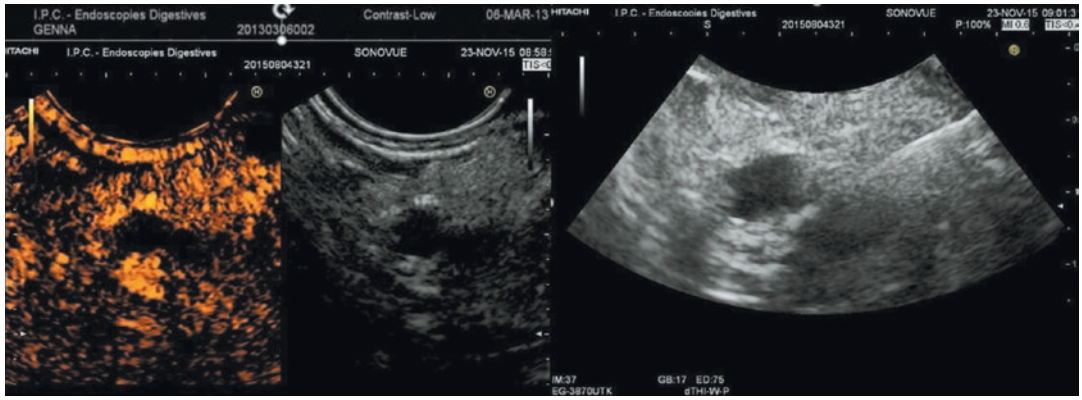

Fig. 3.3 Mural nodule enhancement after intravenous administration of Sonovue® displayed by EUS. EUS-FNA of the mural nodule. Courtesy of Professor Marc Giovannini. Institut Paoli-Calmettes, Marseilles, France

cystic lesion may be helpful in the differential diagnosis between mucinous and non-mucinous cysts [41].

Brush cytology and forceps biopsy are not yet recommended in daily clinical practice requiring these procedures further studies [21].

Finally, in patients unfit for surgery, EUS-guided radio frequency ablation would be a therapeutic option (Fig. 3.4) [42].

Cyst Fluid Analyses The study of cystic fluid obtained after EUS-FNA is evolving and remains investigational for the most part of their parameters. However, currently available data and further initiated research could help in differentiating mucinous from non-mucinous PCN and in the dire challenging clinical decision-making algorithm in detecting high-risk IPMNs. Study of the cyst fluid content encomprises cytology,

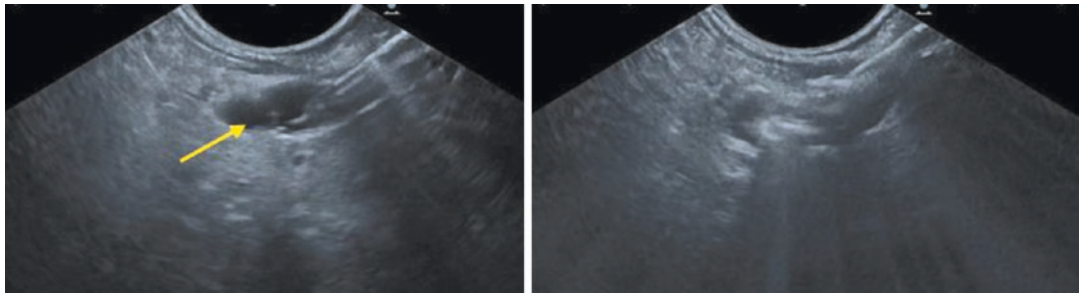

Fig. 3.4 Mural nodule (arrow) of an IPMN treated with EUS-guided RFA. Courtesy of Professor Marc Giovannini. Institut Paoli-Calmettes, Marseilles, France

biochemical analyses of CEA, Ca 19-9, viscosity, amylase/lipase and glucose, mucin stain, and proteomics and molecular analyses.

Cytology of the cystic fluid is of great value in assessing the risk of malignancy in IPMNs, although its sensitivity and specificity are hampered by the low volume, low cellular yield, and interobserver variability. The Moray micro forceps biopsy employed through a 19-gauge needle inserted into the cyst has been statistically significant superior to conventional analyses of the cystic fluid in diagnosing the specific type of the cyst [43]. However, this procedure has not been widely accepted in daily clinical practice.

CEA is the most widely employed protein marker in pancreatic cyst fluid being a valuable tool to distinguish between mucinous from non-mucinous lesions, although it cannot differentiate between benign cysts from those with high-grade dysplasia or invasive carcinoma [44]. CEA cut-off values of 109.9 and 192 ng/mL have been found to have an accuracy value of 79% and 86%, respectively, in detecting mucinous lesions [26]. The cyst fluid Ca 19-9 is not useful in distinguishing benign from malignant PCN [45]. The viscosity of IPMNs is typically thick while amylase levels will be high (>250 U/L). However, some mucinous neoplasms may have high levels of CEA and amylase also. Low levels of amylase neither rule out malignancy [46].

DNA alterations in the cyst fluid, especially mutations of *KRAS* and *GNAS* analyzed by next generation sequencing can distinguish mucinous from non-mucinous cysts [47], specially GNAS has been reported to have a sensitivity of 98% and a specificity of 100% in differentiated IPMNs from mucinous cystic neoplasms [48]. Different subtypes of mucin are released according to the histopathological subtype of IPMNs that also corresponds to the grade of dysplasia [49].

Interleukins levels of IL-1b, IL-5 and IL-8 have been found significantly higher in cysts with high-grade dysplasia or malignancy, being IL-1b the more accurate parameter in predicting high-risk versus low-risk with a sensitivity and specificity of 79% and 95%, respectively [50]. Prostaglandin E2 has been associated with PDA and has been found significantly higher in IPMMs compared to mucinous neoplasms ($p < 0.05$) and their levels correlated in a stepwise manner with the degree of dysplasia of the IPMN in two studies [51, 52].

MicroRNA profiling using Next Generation Sequencing displays aberrant microRNA expression in PDA and pancreatic cysts, being miR-216 the parameter most associated with dysplasia with a statistical difference in high-grade dysplasia-IPMNs and pancreatic cancer associated with IPMNs, when compared to low-grade dysplastic IPMNs [53]. Therefore, microRNA would be of great value in stratifying IPMNs [9].

Colon epithelial protein, when found in gastric and pancreatic epithelium, poses a risk of developing invasive carcinoma and react to the murine Das-1 monoclonal antibody [9, 54]. The dysplastic

changes arising in the epithelial lining of the cysts may produce specific changes in the cystic fluid milieu that could be studied by several methods to investigate panels or a combination of several markers in order to better distinguish between high-risk from low-risk lesions.

To sum up, the study of cystic fluid biomarkers is an evolving field aiming to obtain accurate information to discriminate between high- and low-risk IPMNs leading to a sort of personalized medicine. Cystic fluid biomarkers obtained by EUS-FNA would be integrated into the management guidelines (based only on specific clinical, imaging, and laboratory parameters), helping in the clinical decision-making to timely send to surgery high-risk lesions, avoid high-risk surgical procedures in low-risk lesions that could be also followed-up with this combined approach including cyst fluid analyses.

3.7 Clinical and Surgical Management According to Published Guidelines

IPMNs are frequently found lesions carrying the potential of harboring or developing malignancy that has to be accurately evaluated by high-resolution imaging techniques and EUS to select patients for surgery and apply an adequate surveillance protocol [55].

To fulfil these two goals, several guidelines have been published (Tables 3.2 and 3.3) [21, 25, 38, 56], with differences between them regarding optimal indications for surgery, surveillance protocols, and the decision to stop follow-up [55].

Therefore, appropriate indication for surgery and surveillance will be based on high-risk stigmata/worrisome features balanced with the patient's age/comorbidities.

Table 3.2 Indications for surgery, diagnostic techniques, and management

Guideline	Year	Possible Indications for surgery	Diagnostic technique	Management
IAP I [56]	2006	Symptoms Cyst size ≥3 cm Mural nodule MPD ≥5 mm Positive cytology	CT scan MRI/MRCP EUS + FNA	Surgery
AGA [38]	2015	High risk features – Cyst size ≥3 cm – Presence of solid component – Dilated MPD – HGD or cancer on cytology	(CT scan) MRI/MRCP EUS + FNA	Surgery
IAP III[a] [25]	2017	High risk stigmata – Jaundice – Enhancing mural nodule ≥5 mm – MPD ≥10 mm – HGD or cancer on cytology	(CT scan) MRI/MRCP	Surgery
		Worrisome features – Cyst size ≥3 cm – Acute pancreatitis (due to IPMN) – Enhancing mural nodule <5 mm – Thickened and enhancing cyst wall – MPD dilation 5–9 mm – Abrupt change of MPD calibre with distal pancreatic atrophy – Presence of lymphadenopathy – Elevated serum CA 19–9 – Cyst growth rate >5 mm/2 years	(CT scan) MRI/MRCP EUS + FNA: required after imaging	Surgery versus close surveillance

(continued)

Table 3.2 (continued)

Guideline	Year	Possible Indications for surgery	Diagnostic technique	Management
European [21]	2018	Absolute indications – Jaundice – Enhancing mural nodule ≥5 mm – MPD ≥10 mm – HGD or cancer on cytology – Solid mass	(CT scan) (EUS + FNA) MRI/MRCP	Surgery
		Relative indications – Cyst size ≥4 cm – Enhancing mural nodule <5 mm – MPD dilation 5–9.9 mm – Serum CA 19.9 ≥37 U/ml – Cyst growth rate >5 mm/years – Acute pancreatitis (due to IPMN) – New onset of diabetes	(CT scan) (EUS + FNA) MRI/MRCP	Surgery

Adapted from the International European and American Gastroenterological Association (AGA) guidelines [55]
CT computed tomography, *EUS* endoscopic ultrasound, *FNA* fine needle aspiration, *HGD* high-grade dysplasia, *IAP* International Association of Pancreatology, *IPMN* intraductal papillary mucinous neoplasm, *MPD* main pancreatic duct, *MRCP* magnetic resonance with cholangiopancreatography, *MRI* magnetic resonance imaging
[a]A second revision of the International guidelines was made in 2012; since the guidelines did not change significantly—particularly when considering indications for surgery/surveillance—the last and updated version of the International guidelines has been included in this review

Table 3.3 Different surveillance strategies

Guideline	Year	Indications for surveillance	Methods of follow-up	Timing
IAP I [56]	2006	BD-IPMNs ≤30 mm without – Symptoms – Mural nodules – Positive cytology	MRI/MRCP or CT scan	Cyst size ≤20 mm • Every 6–12 months[a] Cyst size 20–30 mm • Every 3–6 months Lifetime surveillance • The interval follow-up can be outstreched if there are no changes after after a period of 2 years
AGA [38]	2015	BD-IPMNs ≤30 mm without – Solid component – Dilated MPD – HGD or cancer on cytology	MRI	Years 1, 2, 5 from initial diagnosis
IAP III[b] [25]	2017	No high-risk stigmata or worrisome features Cyst size <10 mm	(CT scan) MRI/MRCP	• At 6 months from diagnosis • Every 2 years (if no change)
		No high-risk stigmata or worrisome features	(CT scan) MRI/MRCP	• At 6–12 months from diagnosis • Yearly × 2 years • Every 2 years (if no change)
		No high-risk stigmata or worrisome features Cyst size 20–30 mm	MRI/MRCP EUS	• EUS in 3–6 months • Yearly follow-up alternating EUS and MRI
		No high-risk stigmata Presence of worrisome features including cyst size <30 mm	MRI/MRCP EUS	• Every 3–6 months alternating EUS and MRI
		Lifetime surveillance—consider surveillance discontinuation only in patients who become unfit for surgery		

Table 3.3 (continued)

Guideline	Year	Indications for surveillance	Methods of follow-up	Timing
European [21]	2018	No absolute or relative indications for surgery	MRI/MRCP or EUS Serum CA 19.9	• Every 6 months for the first year • Yearly thereafter
		No absolute indications for surgery One relative indication in patients with significant comorbidities	MRI/MRCP or EUS Serum CA 19.9	• Every 6 months

Adapted from International, European, and American Gastroenterological Association (AGA) guidelines [55]
BD branch duct, *CT* computed tomography, *EUS* endoscopic ultrasound, *FNA* fine needle aspiration, *HGD* high-grade dysplasia, *IAP* International Association of Pancreatology, *IPMN* intraductal papillary mucinous neoplasm, *MPD* main pancreatic duct, *MRCP* magnetic resonance with cholangiopancreatography, *MRI* magnetic resonance imaging
[a]The interval of follow-up can be lengthened after two years of no change
[b]A second revision of the International guidelines was made in 2012; since the guidelines did not change significantly—particularly when considering indications for surgery/surveillance—the last and updated version of the International guidelines has been included in this review

Different studies [57, 58] have demonstrated that, although high-risk stigmata or worrisome features are not observed in the diagnosis, after a median follow-up of 5 years, an important number of patients can develop malignancy or high-risk stigmata.

Finally, The addition of taking into account molecular markers into the management of these lesions would lead to a better individualized making-decision algorithm, especially in identifying high-risk lesions in otherwise patients presenting with low-risk lesions on conventional imaging parameters, being needed controlled studies and refining techniques.

References

1. Adsay V, Mino-Kenudson M, Furukawa T, et al. Pathologic evaluation and reporting of intraductal papillary mucinous neoplasms of the pancreas and other tumoral intraepithelial neoplasms of pancreatobiliary tract: recommendations of verona consensus meeting. Ann Surg. 2016;263(1):162–77.
2. Itai Y, Ohhashi K, Nagai H, et al. "Ductectatic" mucinous cystadenoma and cystadenocarcinoma of the pancreas. Radiology. 1986;161(3):697–700.
3. Klibansky DA, Reid-Lombardo KM, Gordon SR, et al. The clinical relevance of the increasing incidence of intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol. 2012;10(5):555–8.
4. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol. 2008;191(3):802–7.
5. Spinelli KS, Fromwiller TE, Daniel RA, et al. Cystic pancreatic neoplasms: observe or operate. Ann Surg. 2004;239(5):651–7. discussion 7–9
6. Zhang XM, Mitchell DG, Dohke M, et al. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. Radiology. 2002;223(2):547–53.
7. Girometti R, Intini SG, Cereser L, et al. Incidental pancreatic cysts: a frequent finding in liver-transplanted patients as assessed by 3D T2-weighted turbo spin echo magnetic resonance cholangiopancreatography. JOP. 2009;10(5):507–14.
8. Del Chiaro M, Segersvärd R, Pozzi Mucelli R, et al. Comparison of preoperative conference-based diagnosis with histology of cystic tumors of the pancreas. Ann Surg Oncol. 2014;21(5):1539–44.
9. Hao S, Takahashi C, Snyder RA, et al. Stratifying intraductal papillary mucinous neoplasms by cyst fluid analysis: present and future. Int J Mol Sci. 2020;21(3):1147.
10. Kosmahl M, Pauser U, Peters K, et al. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch. 2004;445(2):168–78.
11. Allen PJ, D'Angelica M, Gonen M, et al. A selective approach to the resection of cystic lesions of the pancreas: results from 539 consecutive patients. Ann Surg. 2006;244(4):572–82.
12. Lee CJ, Scheiman J, Anderson MA, et al. Risk of malignancy in resected cystic tumors of the pancreas < or =3 cm in size: is it safe to observe asymptomatic patients? A multi-institutional report. J Gastrointest Surg. 2008;12(2):234–42.
13. Fukushima N, Mukai K. Pancreatic neoplasms with abundant mucus production: emphasis on intraductal papillary-mucinous tumors and mucinous cystic tumors. Adv Anat Pathol. 1999;6(2):65–77.
14. Capurso G, Boccia S, Salvia R, et al. Risk factors for intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a multicentre case-control study. Am J Gastroenterol. 2013;108(6):1003–9.

15. Sato N, Rosty C, Jansen M, et al. STK11/LKB1 Peutz-Jeghers gene inactivation in intraductal papillary-mucinous neoplasms of the pancreas. Am J Pathol. 2001;159(6):2017–22.
16. Maire F, Hammel P, Terris B, et al. Intraductal papillary and mucinous pancreatic tumour: a new extracolonic tumour in familial adenomatous polyposis. Gut. 2002;51(3):446–9.
17. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol. 2009;104(9):2175–81.
18. Buscail E, Cauvin T, Fernandez B, et al. Intraductal papillary mucinous neoplasms of the pancreas and European guidelines: importance of the surgery type in the decision-making process. BMC Surg. 2019;19(1):115.
19. Han Y, Lee H, Kang JS, et al. Progression of pancreatic branch duct intraductal papillary mucinous neoplasm associates with cyst size. Gastroenterology. 2018;154(3):576–84.
20. Lafemina J, Katabi N, Klimstra D, et al. Malignant progression in IPMN: a cohort analysis of patients initially selected for resection or observation. Ann Surg Oncol. 2013;20(2):440–7.
21. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018;67(5):789–804.
22. Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183–97.
23. Sereni E, Luchini C, Salvia R, et al. Molecular and clinical patterns of local progression in the pancreatic remnant following resection of pancreatic intraductal papillary mucinous neoplasm (IPMN). Chin Clin Oncol. 2019;8(2):21.
24. Koshita S, Fujita N, Noda Y, et al. Invasive carcinoma derived from "flat type" branch duct intraductal papillary mucinous neoplasms of the pancreas: impact of classification according to the height of mural nodule on endoscopic ultrasonography. J Hepatobiliary Pancreat Sci. 2015;22(4):301–9.
25. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17(5):738–53.
26. Morales-Oyarvide V, Fong ZV, Fernández-Del Castillo C, et al. Intraductal papillary mucinous neoplasms of the pancreas: strategic considerations. Visc Med. 2017;33(6):466–76.
27. Fritz S, Fernandez-del Castillo C, Mino-Kenudson M, et al. Global genomic analysis of intraductal papillary mucinous neoplasms of the pancreas reveals significant molecular differences compared to ductal adenocarcinoma. Ann Surg. 2009;249:440–7.
28. Wu J, Jiao Y, Dal Molin M, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proc Natl Acad Sci U S A. 2011;108(52):21188–93.
29. Amato E, Molin M, Mafficini A, et al. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. J Pathol. 2014;233(3):217–27.
30. Nasca V, Chiaravalli M, Piro G, et al. Intraductal pancreatic mucinous neoplasms: a tumor-biology based approach for risk stratification. Int J Mol Sci. 2020;21(17):6386.
31. Patra KC, Bardeesy N, Mizukami Y. Diversity of precursor lesions for pancreatic cancer: the genetics and biology of intraductal papillary mucinous neoplasm. Clin Transl Gastroenterol. 2017;8(4):e86.
32. Yamaguchi K, Kanemitsu S, Hatori T, et al. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. Pancreas. 2011;40(4):571–80.
33. Grützmann R, Niedergethmann M, Pilarsky C, et al. Intraductal papillary mucinous tumors of the pancreas: biology, diagnosis, and treatment. Oncologist. 2010;15(12):1294–309.
34. Morales-Oyarvide V, Mino-Kenudson M, Ferrone CR, et al. Diabetes mellitus in intraductal papillary mucinous neoplasm of the pancreas is associated with high-grade dysplasia and invasive carcinoma. Pancreatology. 2017;17(6):920–6.
35. Fritz S, Hackert T, Hinz U, et al. Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas. Br J Surg. 2011;98(1):104–10.
36. Wang W, Zhang L, Chen L, et al. Serum carcinoembryonic antigen & carbohydrate antigen 19-9 for prediction of malignancy and invasiveness in intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. Biomed Rep. 2015;3:43–50.
37. Crippa S, Bassi C, Salvia R, et al. Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis. Gut. 2017;66(3):495–506.
38. Vege SS, Ziring B, Jain R, et al. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):819–22.
39. Fernández-del Castillo C, Adsay NV. Intraductal papillary mucinous neoplasms of the pancreas. Gastroenterology. 2010;139(3):708–13. 13.e1–2
40. Kitano M, Sakamoto H, Komaki T, et al. New techniques and future perspective of EUS for the differential diagnosis of pancreatic malignancies: contrast harmonic imaging. Dig Endosc. 2011;23(Suppl 1):46–50.
41. Napoleon B, Palazzo M, Lemaistre A-I, et al. Needle-based confocal laser endomicroscopy of pancreatic

cystic lesions: a prospective multicenter validation study in patients with definite diagnosis. Endoscopy. 2019;51(09):825–35.
42. Barthet M, Giovannini M, Lesavre N, et al. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. Endoscopy. 2019;51(9):836–42.
43. Zhang ML, Arpin RN, Brugge WR, et al. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. Cancer Cytopathol. 2018;126(6):414–20.
44. Correa-Gallego C, Warshaw AL, Fernandez-del Castillo C. Fluid CEA in IPMNs: a useful test or the flip of a coin? Am J Gastroenterol. 2009;104:796–7.
45. Cao S, Hu Y, Gao X, et al. Serum carbohydrate antigen 19-9 in differential diagnosis of benign and malignant pancreatic cystic neoplasms: a meta-analysis. PLoS One. 2016;11(11):e0166406.
46. Scourtas A, Dudley JC, Brugge WR, et al. Preoperative characteristics and cytological features of 136 histologically confirmed pancreatic mucinous cystic neoplasms. Cancer Cytopathol. 2017;125(3):169–77.
47. Jones M, Zheng Z, Wang J, et al. Impact of next-generation sequencing on the clinical diagnosis of pancreatic cysts. Gastrointest Endosc. 2016;83(1):140–8.
48. Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011;3(92):92ra66.
49. Kim GE, Bae HI, Park HU, et al. Aberrant expression of MUC5AC and MUC6 gastric mucins and sialyl Tn antigen in intraepithelial neoplasms of the pancreas. Gastroenterology. 2002;123(4):1052–60.
50. Maker AV, Katabi N, Qin LX, et al. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. Clin Cancer Res. 2011;17(6):1502–8.
51. Schmidt CM, Yip-Schneider MT, Ralstin MC, et al. PGE(2) in pancreatic cyst fluid helps differentiate IPMN from MCN and predict IPMN dysplasia. J Gastrointest Surg. 2008;12(2):243–9.
52. Yip-Schneider MT, Carr RA, Wu H, et al. Prostaglandin E(2): a pancreatic fluid biomarker of intraductal papillary mucinous neoplasm dysplasia. J Am Coll Surg. 2017;225(4):481–7.
53. Wang J, Paris PL, Chen J, et al. Next generation sequencing of pancreatic cyst fluid microRNAs from low grade-benign and high grade-invasive lesions. Cancer Lett. 2015;356(2, Part B):404–9.
54. Das KK, Geng X, Brown JW, et al. Cross validation of the monoclonal antibody das-1 in identification of high-risk mucinous pancreatic cystic lesions. Gastroenterology. 2019;157(3):720–30.e2.
55. Crippa S, Arcidiacono PG, De Cobelli F, et al. Review of the diagnosis and management of intraductal papillary mucinous neoplasms. United European Gastroenterol J. 2020;8(3):249–55.
56. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1-2):17–32.
57. Crippa S, Pezzilli R, Bissolati M, et al. Active surveillance beyond 5 years is required for presumed branch-duct intraductal papillary mucinous neoplasms undergoing non-operative management. Am J Gastroenterol. 2017;112(7):1153–61.
58. Pergolini I, Sahora K, Ferrone CR, et al. Long-term risk of pancreatic malignancy in patients with branch duct intraductal papillary mucinous neoplasm in a referral center. Gastroenterology. 2017;153(5):1284–94.e1.