Chapter 2
Surveillance and Intervention in IPMN

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More frequent use of high-quality cross-sectional imaging, increased life expectancy, and the trend for healthy individuals to undergo "health checkups," including full-body magnetic resonance imaging (MRI), have increased the detection of intraductal papillary mucinous neoplasm of the pancreas (IPMN) [1]. IPMN is a heterogeneous group of pancreatic cystic neoplasm arising from the proliferation of mucin-producing cells within the pancreatic ducts [2]. IPMN can be morphologically divided into main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN) and mixed-type IPMN (MT-IPMN) on the basis of the anatomical distribution of duct(s) dilatation in the pancreatic gland [3, 4].

IPMN represents 20–50% of all pancreas cystic neoplasms and 1–3% of the exocrine pancreatic neoplasms [5–7]. The male to female ratio reported for IPMN in the population is 3:1 (2:1 for BD-IPMN) [8]. Surprisingly, these ratios seem to vary between countries/regions. A male predominance was observed in Korea and

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C. W. Michalski et al. (eds.), *Translational Pancreatic Cancer Research*,
Molecular and Translational Medicine,
https://doi.org/10.1007/978-3-030-49476-6_2

Japan, while a more even distribution between male and female was observed in the United States and in Europe. The mean age of presentation is in the fifth to seventh decade [9], and the prevalence increases with increasing age of the population [10].

Due to the potential for progression to invasive cancer, patients with IPMN are routinely monitored. The primary goal is to prevent malignancy and/or alleviate symptoms while avoiding unnecessary surgery. Currently, four guidelines, the 2015 American Gastroenterological Association (AGA) [11], the 2017 International Association of Pancreatology (IAP) [10], the 2018 American College of Gastroenterology (ACG) [12], and the 2018 European Study Group on Cystic Tumours of the Pancreas (European) [13], provide recommendations on surveillance and surgical resection based on symptoms and perceived risk of malignancy (Table 2.1).

Classification of IPMN

Radiological Classification

The morphological classification of IPMN in MD-, BD-, and MT-IPMN is based on radiological characteristics. These subtypes harbor a different risk of malignancy, and therefore each requires a specific therapeutic approach (Fig. 2.1).

MD-IPMN can be recognized by the abrupt dilatation of the pancreatic main duct and the presence of mucus together with villous neoplastic component. The dilatation of the pancreatic main duct can be segmental or along the entire duct. For resected MD-IPMN, the mean frequency of advanced neoplasia (invasive cancer or HGD) is 61.6% (range 36–100%), and the mean frequency of invasive cancer is 43.1% (range 11–82%) [14–26].

BD-IPMN is characterized by a "grape-like" dilatation of pancreatic side branch ducts. For resected BD-IPMN, the mean frequency for invasive carcinoma and high-grade dysplasia (HGD) is 31.1% (range 14.4–47.9%), and the frequency of invasive cancer is 18.5% (range 6.1–37.7%) [27–33].

MT-IPMN presents radiological characteristics of both MD- and BD-IPMN. For resected MT-IPMN, the mean frequency of HGD and invasive carcinoma is the same as for MD-IPMN.

Histological Classification

Histologically, IPMN can be divided on the basis of the epithelium in different histologic phenotypes: intestinal, gastric, oncocytic, and pancreatobiliary type. Typically, these distinctions can only be made reliably based on surgical specimens, thus limiting their value in the diagnostic process [34].

Table 2.1 Absolute and relative indications for surgical resection by 2015 AGA, 2017 IAP, 2018 European, and 2018 ACG guidelines

Guidelines	Cyst type	Absolute indications for surgery	Relative indications for surgery
2015 AGA guideline	IPMN	PD ≥ 5 mm (on MRI *and* EUS) *and* solid component *or* cytology positive for malignancy	
2017 IAP guideline	IPMN	Cytology suspicious or positive for malignancy Jaundice (IPMN related) Enhancing mural nodule (≥5 mm) PD dilatation ≥ 10 mm	Grow rate ≥ 5 mm/2 years Increased levels of serum CA 19.9 PD dilatation between 5 and 9 mm Cyst diameter ≥ 30 mm Acute pancreatitis (caused by IPMN) Enhancing mural nodule (<5 mm) Abrupt change in caliber of PD with distal pancreatic atrophy Lymphadenopathy Thickened/enhancing cyst walls
2018 European guideline	IPMN	Positive cytology for malignancy/ HGD Solid mass Jaundice (IPMN related) Enhancing mural nodule (≥5 mm) PD dilatation ≥ 10 mm	Grow rate ≥ 5 mm/year Increased levels of serum CA 19.9 (>37 U/m) * PD dilatation between 5 and 9.9 mm Cyst diameter ≥ 40 mm New onset of diabetes mellitus Acute pancreatitis (caused by IPMN) Enhancing mural nodule (<5 mm)
2018 ACG guideline	IPMN	Decided by multidisciplinary team Referral in case of: Jaundice (IPMN related) Acute pancreatitis (caused by IPMN) Increased levels of serum CA 19.9 Mural nodule/solid component PD dilatation > 5 mm Cyst diameter ≥ 30 mm Positive cytology for malignancy/ HGD	

ACG American College of Gastroenterology, *AGA* American Gastroenterological Association, *CA 19.9* cancer antigen 19.9, *EUS* endoscopic ultrasound, *HGD* high-grade dysplasia, *IAP* International Association of Pancreatology, *IPMN* intraductal papillary mucinous neoplasm, *MRI* magnetic resonance imaging, *PD* pancreatic duct

*The 2015 AGA guideline suggests to discontinue the follow-up after 5 years, if there is no change in size or characteristics of the cyst

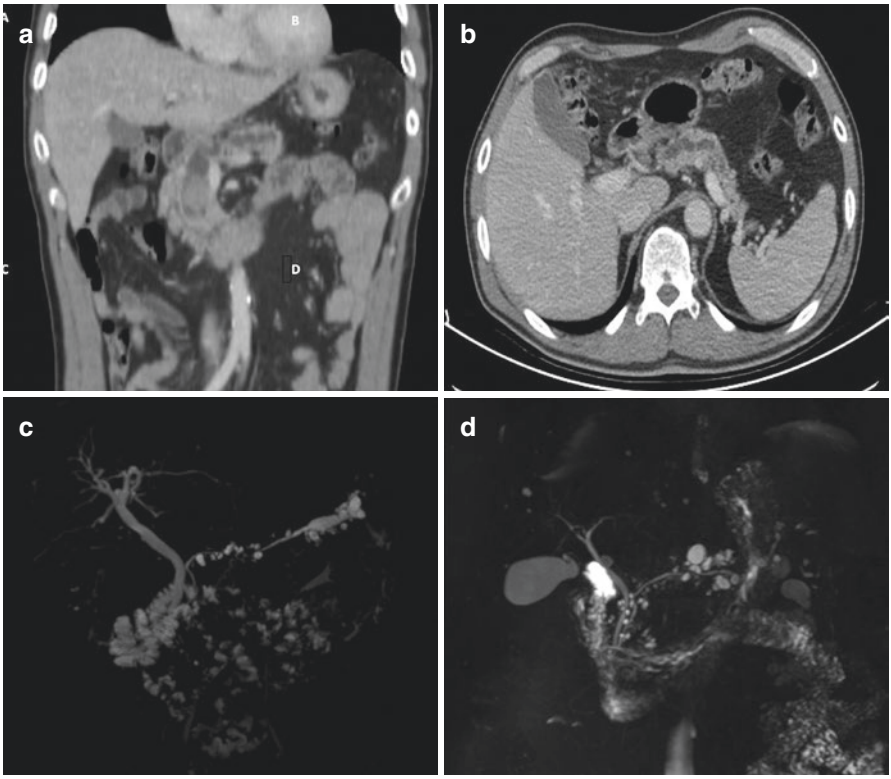

Fig. 2.1 Different types of IPMN. (**a**) BD-IPMN with slender MPD in the tail. (**b**) Both dilated MPD and BD in the pancreatic tail, image matching a MT-IPMN. (**c**) Dilated MPD in the head of the pancreas. (**d**) Image matching a MD-IPMN with solid component as a sign of a possible malignant degeneracy

Further distinction is based on cytological and architectural atypia in noninvasive IPMN. Currently, the World Health Organization (WHO) classification recommends a three-tiered system for grading of dysplasia in IPMN, from low- to high-grade dysplasia [35].

Low-grade dysplasia (LGD) is characterized by cells with oriented nuclei with small variability in nuclear size, shape, and retained polarity. *Moderate-grade* dysplasia is defined by nuclear pleomorphism, increased nucleus-to-cytoplasm ratio, and nuclear pseudostratification. *High-grade* dysplasia (HGD) features architectural complexity and marked variability in nuclear size and shape [36]. In order to improve the concordance of reporting and alignment with practical consequences, a two-tiered grading system has been proposed (low- versus high-grade dysplasia) [37].

Regarding the histological classification of IPMN, *gastric*-type IPMN is characterized by low-grade dysplasia and abundant cytoplasmic mucin that expresses *MUC-5AC*. When the gastric type has invasive characteristics and is localized in the pancreatic main duct, it is more likely a more aggressive tubular carcinoma [38].

The *intestinal epithelial* type [39] is the most common in IPMN and resembles normal intestinal epithelial cells with expression of *MUC-2* and *CDX-2*. *The pancreatobiliary*-type IPMNs express MUC-1, and in this type, cells are organized as complex papillae. This subtype is associated with invasive carcinoma in 90% of patients. The pancreatobiliary subtype is also associated with invasive tubular adenocarcinoma, and both morphology and prognosis are similar to PDAC (pancreatic ductal adenocarcinoma) [40–42]. The *oncocytic*-type IPMN is characterized by cells with abundant eosinophil cytoplasm rich in mitochondria organized in complex papillae or solid sheets and severe high-grade dysplasia [43].

IPMN can contain more than one subtype, and it is recommended to report the dominant subtype and/or the subtype exhibiting the highest degree of dysplasia. The oncocytic type occurs only in a "pure" form, without mixing with other different histological subtypes [40, 41]. A 2011 study classified 283 surgically resected IPMNs: 137 BD-IPMNs, 102 MD-IPMNs, and 44 MT-IPMNs. Among these, 139 patients had gastric type (90 patients with BD-IPMN, 34 with MD-IPMN, and 15 with MT-IPMN), 101 patients had intestinal type (28 patients with BD-IPMN, 54 with MD-IPMN, and 19 with MT-IPMN), 24 patients had oncocytic type (12 patients with BD-IPMN, 8 with MD-IPMN, and 4 with MT-IPMN), and 19 had pancreatobiliary type (7 with BD-IPMN, 6 with MD-IPMN, and 6 with MT-IPMN) [41]. These findings are supported by other studies [40, 44] and demonstrate that the gastric and intestinal subtypes are the most common and that all histopathological subtypes can be found in the three morphological imaging-based subtypes (BD-, MD-, MT-IPMN).

Intraductal tubulopapillary neoplasm (ITPN) is a rare intraductal epithelial neoplasm of the pancreas recently recognized as a distinct entity by the WHO classification in 2010. It accounts less than 1% of all pancreatic exocrine neoplasms and the 3% of intraductal pancreatic neoplasms. Compared to IPMN, they are less often cystic, typically mass forming, without overt production of mucin. ITPNs typically have uniform high-grade dysplasia, and approximately 40–50% of the cases are associated with invasive cancer [45, 46]. ITPN is often difficult to differentiate histologically from IPMN, especially the pancreatobiliary and oncocytic subtype. ITPNs showed positive for cytokeratin, CK19, MUC1, and MUC6 at the immunohistochemistry analysis [47].

Diagnosis

Symptoms

Most IPMNs do not cause symptoms. In case of symptoms, the most common are weight loss, pancreatitis, jaundice, palpable mass, and postprandial fullness according to a study from a high-volume center. Only pancreatitis and jaundice could be related to the presence of IPMN [48]. Main duct IPMN is more often symptomatic than branch duct IPMN. This can be related to the massive production of mucin in MD-IPMN;

mucin plugs may occlude the pancreatic duct and lead to acute pancreatitis with epigastric discomfort. These symptoms have been reported in approximately 25% of patients with MD-IPMN [49, 50]. The chronic obstruction of the outflow of pancreatic juice can lead to pancreatic endocrine and exocrine insufficiency and resulting diabetes, diarrhea, and steatorrhea. Jaundice can be secondary to mucin plugs in the distal bile duct or direct tumor invasion in case of malignant progression.

Symptoms, such as acute pancreatitis, jaundice, or new-onset of diabetes mellitus, are mostly associated with high-grade dysplasia or invasive carcinoma [51, 52]. These symptoms in the presence of an IPMN have been part of the IAP and European criteria in the predictive factors for malignant IPMN [9, 46, 53].

Imaging Techniques

Currently, cross-sectional imaging plays a central role in lesion detection and differentiation of IPMN. The presence and extent of IPMN can be assessed with computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS). Gadolinium-enhanced magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) is the modality of choice, because of its superiority in identifying a connection between the MDP and the lesion and mural nodules and septations, as well as cyst differentiation [10, 54]. In addition, studies have shown that repeated exposure to ionizing radiation following CT increases the risk of malignancy. Therefore MRI/MRCP, avoiding the ionizing radiations, is the preferred method for surveillance of PCN (pancreatic cystic neoplasm) [1]. By definition, branch duct IPMNs have a communication to the main pancreatic duct that can be best assessed with either MRI (90–100%) or EUS (80–90%) [55]. For MD-IPMN and MT-IPMN, a focal or diffuse involvement of the main pancreatic duct can easily be assessed by MRI/MRCP and EUS. A systematic review reported that CT is able to correctly differentiate benign from malignant cysts with 71–80% accuracy and a presence of a communication between the cyst and the pancreatic duct with 80% accuracy; for MRI and MRCP, these were 55–76% and 96% [56]. Another systematic review including 37 studies observed a pooled 81% sensitivity and 76% specificity for risk features predictive of malignancy on CT/MRI [57]. Higher accuracy can be observed with EUS, with a 65–96% accuracy to detect benign from malignant cyst, but due to its invasive nature, it should be reserved for selected cases [58].

Cyst Fluid Analysis and Biomarkers

EUS allows fine needle aspiration (FNA) of the cyst fluid. EUS-FNA is a safe procedure. In a retrospective study in two experienced academic institutions, the complication rate of EUS in 603 patients was 2.2% with pancreatitis, abdominal pain, retroperitoneal bleeding, infection, and bradycardia as main complications [59].

A cyst fluid CEA (carcinoembryonic antigen) with a cutoff of 192–200 ng/ml [4, 60], as well as amylase, can be helpful in the differential diagnosis of pancreatic cysts and grade of dysplasia. CEA level showed to have 52–78% of sensitivity and 63–91% of specificity for identifying IPMN and MCN [13, 61, 62].

Cytology may report on low- and intermediate-grade dysplasia, high-grade dysplasia, or invasive carcinoma [63]. It is, however, common to find different grades of atypia within the same lesion; therefore the cytological examination of IPMN is not enough to assess the entire cytological pattern of the cystic lesion. Matthaei et al. [64] reported that the analysis of cells in the cystic fluid allowed to detect invasive carcinoma and HGD with 72% of sensitivity and positive predictive value (80% accuracy).

DNA-based testing of pancreatic cyst fluid seems to be a promising adjunct for the differentiation between mucinous and non-mucinous PCN, between mucinous PCNs (IPMN versus MCN), and between premalignant PCNs and those with advanced neoplasia. Many genetic mutations have been reported regarding IPMN: KRAS (~80% of IPMN), GNAS (~70% of IPMN), RNF43, PIK3CA, p16/CDKN2A, SMAD4, and Tp53 [65, 66]. The mutation of GNAS and KRAS is seen in >90% of IPMN [66, 67], and GNAS mutation is more common in intestinal-type IPMN [66, 68].

From recent genetic studies, it is clear that both invasive and noninvasive components tend to harbor identical mutations [65, 66]. In the near future, micro-RNA might be the key to distinguish IPMN from other cysts of the pancreas and even discern low-grade IPMN from high-grade dysplasia IPMN [68–70]. Moreover glycoprotein altered expression in the cystic fluid might be useful as well in differentiating IPMN with low-grade dysplasia from high-grade IPMN [71–73].

New Developments in Imaging Techniques

Recent evidence suggests that MRCP (thick and thin T2 slices, centered on the main pancreatic duct at the head and body/tail level) or CT scan with slices <2 mm width (three phases: no iodine IV contrast, arterial, and portal phases) should be used when evaluating a pancreatic cyst [1, 10]. EUS should remain a third option for those cases in whom the radiographic characterization of the pancreatic lesion is unclear [74]. Nevertheless, EUS is very useful to detect mural nodules, especially when the examination is integrated with a contrast-enhanced endoscopic ultrasound (CH-EUS) [75]. Contrast-enhanced EUS (CE-EUS) can be used to better differentiate a mucin plug and mural nodule using echo-Doppler during the examination, and even better definition can be assessed with tissue harmonic echo (THE) [76]. Nevertheless, EUS is an operator-dependent procedure that relies on the specialist's experience and ability.

More recently, a new endoscopic modality has been described, the needle-based confocal laser endomicroscopy (nCLE) that can provide a real-time in vivo optical biopsy with the use of a fluorescent dye [77]. The nCLE has been proven feasible and reliable in differentiating SCN from mucinous lesions [78–82].

The micro-forceps biopsy (MFB) is showing good results in the assessment of the nature of pancreatic cysts. The device can be inserted in a 19 gauge needle during the endoscopy procedure and allow a "micro-biopsy" from the cyst wall or septations for histological evaluation of the cyst architecture and subepithelial stroma. The MFB can be used in addition to the pancreatic cyst fluid (PCF) examination and in a recent paper by Zhang et al. [83] has proven good result in diagnosing specific type of pancreatic cyst, with consequent important implications regarding the management of the patients. The presence of epithelial stroma in the biopsy performed with the micro-forceps can help the pathologist in the differential diagnosis between MCN and IPMNs [83].

Another technique to identify and characterize pancreatic IPMNs is the peroral pancreatoscopy (POPS) [84]. The added value of this technique appears to lie in the ability to identify pancreatic duct skip lesions (reported in about 6–19% of the patients [85]) in order to reduce recurrences after pancreatic surgery [86]. In addition, POPS allows collection of pancreatic juice for cytopathological examination and for biopsy using the mini-forceps.

Clinical and Radiological Characteristics Associated with Advanced Neoplasia

Many guidelines have been published on management of pancreatic cystic neoplasms (PCNs): the IAP (2017) guideline for the management of IPMN of the pancreas [10], the European evidence-based guideline (2018) on pancreatic cystic neoplasms [54], the AGA guideline (2015) [87], and the ACG clinical guideline (2018) [88].

According to both the IAP and European guidelines, jaundice, the presence of an enhancing mural nodule ≥5 mm, the presence of a solid component, positive cytology, and a dilated PD ≥ 10 mm are highly predictive of advanced neoplasia and therefore an absolute indication for resection in surgically fit patients. According to both the 2017 IAP and the 2018 European guidelines, acute pancreatitis caused by IPMN, an enhancing mural nodule <5 mm, a dilated PD between 5 and 9.9 mm, and an increased level of serum CA19.9 without jaundice are associated with advanced neoplasia in IPMN and therefore a relative indication for surgery in patients fit for surgery.

According to the 2017 IAP guideline, a thickened or enhancing cyst wall, lymphadenopathy, an abrupt change in caliber of PD with distal pancreatic atrophy, grow rate of the cyst of 5 mm or more in 2 years, and a cyst diameter of 30 mm or more are also associated with advanced neoplasia in IPMN. According to the 2018 European guideline, a cyst growth rate of 5 mm or more in 1 year, new onset of diabetes mellitus, and a cyst diameter of 40 mm or more are associated with advanced neoplasia in IPMN. Increased risks of high-grade dysplasia or cancer are also a MPD (main pancreatic duct) between 5 and 9.9 mm, a cystic growth rate

>5 mm/year, serum CA19-9 > 37 U/mL, symptoms, enhancing mural nodules (<5 mm), and/or a cystic diameter >40 mm.

Treatment

When an IPMN at high(er) risk of malignancy is characterized, the treatment of choice is surgery, in surgically fit patients. All guidelines recommend that surgical resection for IPMN should only be performed by experienced surgeons in high-volume centers after consultation by a multidisciplinary team with pancreatic expertise. Standard treatment recommended is pancreatoduodenectomy or left pancreatectomy according to the site and the extent of the disease with lymphadenectomy [10]. Minimally invasive surgery, especially when distal pancreatectomy is indicated, is mostly feasible with good outcome. Most guidelines consider a total pancreatectomy unnecessarily aggressive, especially considering the total endocrine and exocrine insufficiency. For MD-IPMN there is no consensus regarding the best surgical option (total pancreatectomy and partial pancreatectomy followed by close surveillance are possible strategies) [89–93]. In patients with multifocal BD-IPMN, only high-risk BD-IPMN should be resected during surgery, while the other cystic lesions can undergo follow-up. Every cyst should be evaluated individually regarding the presence of sign of degeneration and/or malignancy [13]. The risk of degeneration in multifocal BD-IPMN seems not to be higher compared to the unifocal BD-IPMN (conflicting results can be seen in published literature [14, 94]); therefore a more aggressive approach might be beneficial only in patients with a family history of PDAC [95].

All current guidelines emphasize the importance of intraoperative frozen section. IPMNs originate from pancreatic ducts, both MPD or peripheral ducts; thus the anatomopathological analysis of resection margins and confirmation of disease-free margins are mandatory for radical surgery. This aspect relates very well for those patients with MT-IPMN misdiagnosed as BD-IPMN before surgery, showing involvement of MPD in the pathological examination. When low-grade dysplasia is present in the frozen section, no further resection is required [96]. Obviously, a frozen section will not compensate for potential skip lesions in the MPD [86, 97, 98].

Surveillance After Pancreatectomy

After surgical resection of IPMN, lifelong follow-up and surveillance are recommended because both new IPMN and concomitant PDAC might occur after surgical resection. Resected IPMN-associated cancer should be followed up in the same way as patients with PDAC after pancreatectomy [99].

The main risks of recurrence in patient undergoing surgery for IPMN are HGD (17% of recurrence after surgery [92]) and family history of PDAC (23% of recurrences vs 7% in patients without family history of PDAC [92]). The debate regarding the surgical margins is still open: while Marchegiani et al. [18] found a significantly higher incidence of recurrence in patients with positive margins after surgical resection, He et al. [92] and Kang et al. [100] didn't report any difference in recurrence rate in the positive margins. The risk of recurrence might be correlated not only to other surgical technique but also to the nature of the IPMN and the subtype of the cystic lesion [101–103].

The IAP guideline recommends follow-up at least twice a year for patients with family history of PDAC, surgical resection margin with HGD, and non-intestinal subtype of IPMN. In all other patients with resected IPMN, follow-up every 6–12 months is mandatory. In contrast, the European guideline advises follow-up every 6 months for the first 2 years, followed by yearly surveillance for IPMN with HGD or main duct involvement. All the others should be followed up in the same way as non-resected IPMN.

Recent series underline the increasing risk of recurrence during the surveillance: 4% after 1 year, 25% after 5 years, and 62% after 10 years [92]; the risks of developing a new invasive IPMN are 0%, 8%, and 38% after 1-, 5-, and 10-year follow-up [100]; concomitant PDACs have a cumulative 5- and 10-year incidence of developing of 4.5% and 5.9%, respectively [103]. Therefore, most of the guidelines agree that the surveillance of the patients should not be discontinued if the patient remains fit for surgery.

In some cases, synchronous and metachronous malignancies can be observed during the follow-up of patients with IPMN (20–30% [104]), but the incidence of extra-pancreatic malignancies might be the same with the incidence of cancer in the general population since the percentage of incidence differs from region to region [105].

Surveillance

Follow-up is recommended for all the patients feasible for surgery, without hard indications for resection. Timing of follow-up and the best radiological examination are still a matter of debate. Therefore, the guidelines vary somewhat in their advice.

According to the revised IAP guidelines, an additional EUS is indicated for further inspection of the PCN in patients with clinical or radiological characteristics associated with advanced neoplasia (relative indications for resection) [10]. If on endoscopic ultrasound, hard indications for resection can be ruled out (i.e., enhancing nodule ≥5 mm, PD ≥ 10 mm, cytology suspicious for HGD/invasive cancer), follow-up is advised. The surveillance interval is established on the basis of the main cyst size (Table 2.2): for cyst <1 cm, CT/MRI in 6 months and then every 2 years if there is no change in cyst characteristics and for cyst 1–2 cm, CT/MRI every 6 months for 1 year, then yearly for 2 years, and every 2 years if no change is seen; patients with cyst of 2–3 cm should undergo EUS in 3–6 months and then 1

Table 2.2 Surveillance interval of non-resected PCN stratified by AGA, IAP, and the European guidelines

Guidelines	Cyst type	Cyst size	Surveillance interval	Surveillance modalities
2015 AGA	IPMN	<3 cm	Yearly for 1 year Every 2 years[a]	MRI/MRCP
2017 IAP	IPMN	<1 cm	In 6 months Every 2 years	CT or MRI/MRCP CT or MRI/MRCP
		1–2 cm	Every 6 months for 1 year Yearly for 2 years Every 2 years	CT or MRI/MRCP CT or MRI/MRCP CT or MRI/MRCP
		2–3 cm	3–6 months Yearly	EUS Alternating MRI with EUS
2018 European	IPMN	<4 cm	Every 6 months for 1 year Yearly	CA 19.9, EUS and/or MRI
2018 ACG	IPMN	<1 cm	Every 2 years	MRI
		1–2 cm	Yearly	MRI
		2–3 cm	6–12 months	MRI or EUS

ACG American College of Gastroenterology, *AGA* American Gastroenterological Association, *CA 19.9* cancer antigen 19.9, *CT* computed tomography, *EUS* endoscopic ultrasound, *IAP* International Association of Pancreatology, *IPMN* intraductal papillary mucinous neoplasm, *MRI* magnetic resonance imaging

[a]The 2015 AGA guideline suggests to discontinue the follow-up after 5 years, if there is no change in size or characteristics of the cyst

per year (EUS and MRI can be eventually alternated), and surgery should be considered for young and fit patients who require a prolonged follow-up.

The European guideline [13] recommends follow-up for BD-IPMN < 4 cm without other risk factors with CA19.9 and MRI/MRCP or EUS every 6 months the first year after diagnosis and yearly thereafter.

The best surveillance modality and timing should be evaluated in a large prospective study, possibly within the scope of the PACYFIC study. The PACYFIC study is an international, prospective cohort study aiming to optimize pancreatic cystic neoplasm surveillance (clinical trial number: NTR4505).

During follow-up the 5-year cumulative incidence of developing a concomitant PDAC in patients with IPMN ranges from 2.2% to 8.8% [10]. The follow-up of the patients should be performed with the same radiological technique if possible in order to lower the bias of interobserver measurement of the pancreatic cyst [106].

Conclusions and Recommendations

The detection of pancreatic IPMNs due to the higher rate of radiological examinations and increased life expectancy in the population has led to a global awareness of this entity. Current diagnostic techniques allow to detect and characterize pancreatic cysts, but the natural history of this pathology is still mainly unknown.

Many guidelines have been published and revised in recent years, but the management and surveillance for patients with IPMN remain contradictory.

IPMNs represent a true challenge nowadays, and due to the heterogeneity of these cysts, we truly believe that a multidisciplinary team, and a referred institute, should be mandatory in the decision-making process for these patients. The risk is to underestimate the potential of malignancy of some cystic lesions, leading to a progression of the cyst degeneration with consequent metastasis or invasion of adjacent organs; on the other hand, a too aggressive policy might expose the patients to unnecessary risks of undergoing surgery (morbidity and mortality rates up to 50% and 6.7%, respectively, in high-volume centers) [107] instead of a surveillance program.

Nowadays many questions are still unsolved. For instance, what are the optimal surveillance program and the timing for radiological examination in patients with IPMNs? Which size of BD-IPMN should be considered as indication for surgery and for which size surveillance should not be mandatory? When is better to perform a total pancreatectomy rather than partial pancreatectomy for MD-IPMN?

Further studies and randomized controlled trial are needed to enlighten these aspects since most literature on IPMN is based only on surgical series.

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