Pancreatology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas

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ARTICLE INFO

Article history:
Received 14 August 2023
Received in revised form
14 November 2023
Accepted 22 December 2023
Available online xxx

Keywords:
Guidelines
Intraductal papillary mucinous neoplasm
Pancreatic cancer
Surveillance
International Association of Pancreatology

ABSTRACT

This study group aimed to revise the 2017 international consensus guidelines for the management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas, and mainly focused on five topics; the revision of high-risk stigmata (HRS) and worrisome features (WF), surveillance of non-resected IPMN, surveillance after resection of IPMN, revision of pathological aspects, and investigation of molecular markers in cyst fluid. A new development from the prior guidelines is that systematic reviews were performed for each one of these topics, and published separately to provide evidence-based recommendations. One of the highlights of these new "evidence-based guidelines" is to propose a new management algorithm, and one major revision is to include into the assessment of HRS and WF the imaging findings from endoscopic ultrasound (EUS) and the results of cytological analysis from EUS-guided fine needle aspiration technique, when this is performed. Another key element of the current guidelines is to clarify whether lifetime surveillance for small IPMNs is required, and recommends two options, "stop surveillance" or "continue surveillance for possible development of concomitant pancreatic ductal adenocarcinoma", for small unchanged BD-IPMN after 5 years surveillance. Several other points are also discussed, including identifying high-risk features for recurrence in patients who underwent resection of non-invasive IPMN with negative surgical margin, summaries of the recent observations in the pathology of IPMN. In addition, the emerging role of cyst fluid markers that can aid in distinguishing IPMN from other pancreatic cysts and identify those IPMNs that harbor high-grade dysplasia or invasive carcinoma is discussed.
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1. Introduction

In 2006, the International Association of Pancreatology (IAP) published the first guidelines for the management of IPMN and mucinous cystic neoplasms [1]. These guidelines have been revised in 2012 [2] and in 2017 [3]. A new meeting was held on July 7th,

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https://doi.org/10.1016/j.pan.2023.12.009
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Please cite this article as: T. Ohtsuka, C. Fernandez-del Castillo, T. Furukawa *et al.*, International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas, Pancreatology, https://doi.org/10.1016/j.pan.2023.12.009

2022 in Kyoto, Japan, during the 26th meeting of IAP, with the purpose of creating revised guidelines. Prior to the meeting, five working groups were given the task to review specific topics regarding IPMN and its management and to perform a systematic review of the existing evidence. The results of these reviews were presented in Kyoto and feedback via e-mail was gathered from the audience. The five topics on which the systematic reviews to collect evidence were (1) revision of high-risk stigmata (HRS) and worrisome features (WF) [4], (2) surveillance protocol for non-resected IPMN [5], (3) surveillance after resection of IPMN [6], (4) revision of pathological aspects [7], and (5) investigation of molecular markers in cyst fluid [8]. These systematic reviews are published separately and are being used as references for this guideline [4–8]. Although most of the studies on IPMN do not provide high-level evidence, the present guidelines are noted as "evidence-based guidelines".

One of the main objectives of the current revision was to update the management algorithm. Although the working group is not recommending that endoscopic ultrasound (EUS) be done in every case, and also recognizes that it cannot be performed at the same level in every institution, given that the results are strongly dependent on the expertise of the operators and resources for adequate cytological and molecular analysis if a fine-needle aspiration is performed. However, one major revision in the guidelines is to include the imaging findings of EUS/contrast-enhanced EUS (CE-EUS) and cytology results obtained by EUS-guided fine needle aspiration (EUS-FNA) technique into the assessment of HRS and WF, because EUS has now been accepted as an important modality to evaluate many pancreatic diseases, including pancreatic cysts and IPMN, especially to look for findings suggestive of high-grade dysplasia (HGD)/invasive carcinoma (IC) such as confirming the presence of a mural nodule and its size, in addition to providing an opportunity to sample cyst fluid or do biopsies of solid components [1–3,9,10]. Two additional revisions are to simplify the surveillance protocol of non-resected IPMN and offering the possibility of stopping surveillance for small branch duct IPMN (BD-IPMN) that remains stable for a period of 5 years, with the caveat that concomitant pancreatic ductal adenocarcinoma (PDAC) (i.e carcinoma that does not arise within IPMN) will always remain a possibility, and therefore the clinician and the patient may elect to continue surveillance. Selected clinical questions and recommendations are listed with evidence levels graded according to the SIGN classification [11] in Table 1.

All the authors contributed equally to the guidelines. T Ohtsuka and C Fernandez-del Castillo chaired the international meeting during IAP in Kyoto 2022, and played a pivotal role in the preparation of this manuscript. The remaining authors are listed in alphabetical order.

2. Incidence of pancreatic cysts

Increased use and recent advances in radiological diagnostic modalities have led to frequent identification of incidentally-diagnosed pancreatic cysts including IPMNs. With an incidence of 1.2–2.6 % on CT, and 2.4–49.1 % on MRI [12–17]**.** Population-based incidences of pancreatic cyst are reported to be 2.6 % in Germany [17] and 2.2 % in Korea [16], and the incidence increases with age [16,17]. Tanaka et al. also demonstrated that the incidences of IPMN based on abdominal ultrasound screening were 0 % in 20's and 0.2 % in 30's, and increased to 6.6 % in 70's [18]. Around 80 % of incidental-discovered cysts are considered to be BD-IPMN [16,18], and the role of the guidelines is to identify the high-risk among huge numbers of presumed IPMNs within a framework that considers healthcare economic perspectives, especially in older patients.

3. Classification

The present guidelines continue to use the definitions of the classification of IPMN in the consensus guidelines 2017 based on imaging first (Fig. 1) [1,19], and then, for those that undergo surgical resection, based on pathology. A pancreatic cyst of >5 mm in diameter that communicates with the main pancreatic duct (MPD) is considered as BD-IPMN, although a pseudocyst should be ruled out in patients with a history of acute pancreatitis or trauma. Management of asymptomatic pancreatic cysts $\leq$ 5 mm remains controversial [20,21]; however, for the time being further surveillance is still recommended. Main duct IPMN (MD-IPMN) is characterized by segmental or diffuse dilation of the MPD of >5 mm without other causes of MPD obstruction. Mixed IPMN meets the criteria for both BD-IPMN and MD-IPMN [1].

Classification is important to determine the management of IPMN. The mean rates of HGD/IC in resected BD-IPMN and MD-IPMN are 31 % (15–48 %) and 62 % (36–100 %), respectively, and among them, the rates of IC are 19 % (6–38 %) and 43 % (11–81 %), respectively [3]. In considering the large number of unresected indolent BD-IPMNs, the real rate of HGD/IC of the total number of BD-IPMNs is therefore much lower, and thus, MD-IPMN has a markedly higher risk of HGD/IC than BD-IPMN.

Since the introduction of these definitions of the classification of IPMN in consensus guidelines 2012 [2], many IPMNs have been classified as mixed IPMN, particularly in resected cases [22,23], while the significance of mixed IPMN remains unclear because most mixed IPMNs are indeed BD-IPMNs with MPD dilation mainly due to viscous mucin hypersecretion. On the other hand, there are many BD-IPMNs with pathological involvement of MPD by neoplastic cells without significant MPD dilation, which are categorized as BD-IPMN on imaging but are truly a mixed IPMN on pathology. Although there still exists discrepancy between mixed IPMN diagnosed on imaging and that on pathology, it appears to be difficult to clearly state the significance of classification of mixed IPMN, and therefore, these categorizations are left unchanged at this time.

4. Pathological aspects

4.1. Grade of dysplasia

IPMN microscopically demonstrates papillary growth of columnar neoplastic cells with mucin hypersecretion. IPMNs are graded pathologically as those with low grade dysplasia (LGD), HGD, and IC [24]. HGD is equivalent to "carcinoma in situ" **(CQ4-1)** [3]. Surgical indication will be determined according to the degree of suspicion for components of HGD or IC during diagnostics. The term "malignancy" is used for both IPMNs with HGD and those with IC in several reports; however, in the Verona consensus statements [25], the term "malignancy" is recommended to be used only for IPMN with IC to express its aggressive behavior. Hence in the current guidelines, the term "malignancy" should be discouraged to avoid confusion, which is in line with the previous 2017 version **(CQ4-1)** [3]. It is also strongly recommended that neoplastic components of HGD and IC should be reported separately.

4.2. Morphological subtype

IPMNs are classified into 3 morphological subtypes, namely, gastric, intestinal and pancreatobiliary (Fig. 2). These IPMN subtypes are associated with the postoperative prognosis, i.e., patients with gastric-type IPMNs are most often low-grade BD-IPMNs with the most favorable prognosis, followed by intestinal-type IPMNs, and then, pancreatobiliary type IPMNs with the highest risk of

Table 1
Clinical questions and recommendations.

	Clinical questions	Recommendations	Evidence level[a]	Grade[a]
Revision of "high risk stigmata (HRS)" and worrisome features (WF)" (CQ1)				
CQ1-1	How to differentiate between a mural nodule or solid component?	It is difficult to clearly distinguish between a mural nodule (MN) and a solid component (SC) in the preoperative imaging of IPMN. In practice, both findings of MN and SC are addressed as a high-risk finding in IPMN.	2+	C
CQ1-2	What are the static and dynamic features of mural nodules to be considered as WF and HRS?	Most reports have suggested a MN size of 5−10 mm as an optimal cutoff for the diagnosis of IPMN with high grade dysplasia (HGD)/invasive carcinoma (IC). It is weakly recommended a finding of enhancing MN ≥ 5 mm as HRS.	2++	C
CQ1-3	What are the static and dynamic features of size and characteristics of main pancreatic duct (MPD) to be considered as WF and HRS?	Although the diagnostic performance of MPD diameter alone is not high, the odds ratio in diagnosing IPMN with HGD/IC tends to be high when MPD ≥10 mm is adopted. Therefore, it is weakly recommended to stay MPD ≥10 mm as HRS and 5−9 mm as WF.	2+	C
CQ1-4	What are the static and dynamic features of size of cyst to be considered as WF and HRS?	The average cyst diameter of malignant IPMN is reported to be 30−40 mm in size, and it is weakly recommended to adopt factors with a cyst diameter ≥30 mm as WF. It is recommended to accept "cyst diameter growth rate of 2.5 mm/year or more" as a WF factor.	2+	C
CQ1-5	What are the implications of multiple WF or HRS?	The number of HRS and WF adds to the likelihood of HGD/IC. If multiple factors in HRS/WF are positive, it is weakly recommended to carefully consider indications for surgery by using diagnostic tools such as nomograms.	2-	C
CQ1-6	What is the role of endoscopic ultrasonography (EUS) for the diagnosis of HGD/IC of IPMN?	EUS, including EUS-guided fine needle aspiration (FNA) and contrast-enhanced EUS, is recommended in cases of IPMN with suspicious of HGD/IC if the clinical setting is available.	2++	C
Surveillance of non-resected IPMN (CQ2)				
CQ2-1	Are size criteria helpful to determine surveillance period?	Surveillance protocol including period should be optimized according to the cyst size considering different growth rate and time to progression.	2++	B
CQ2-2	How often should surveillance be carried out?	A surveillance interval of 18, 12, and 6 months for branch duct IPMN (BD-IPMN) measuring <20mm, ≥20mm and <30mm, and ≥30mm respectively, following an initial short-term (6 months) follow-up is recommended.	2+	B
CQ2-3	When should surveillance be discontinued?	Surveillance may be discontinued for patients with cysts <20mm showing no morphological changes and no WF after 5-years of surveillance, with consideration of patient condition and life expectancy. The recommendations for discontinuation of surveillance may not be applicable to younger patients with BD-IPMN and in those with familial or genetic risk as the risk of pancreatic cancer appears to be cumulative over time.	2+	C
CQ2-4	Is nomogram predicting HGD/IC useful during surveillance?	Nomograms could be useful tools in predicting HGD/IC of IPMN during surveillance, by providing a non-invasive and comprehensive interpretation of clinical and radiological features. However, additional studies and new methods will be required to enhance the diagnostic accuracy of HGD/IC prediction.	2+	C
Surveillance after resection of non-invasive IPMN (CQ3)				
CQ3-1	What is the purpose of postoperative surveillance after resection of non-invasive IPMN?	Patients who have undergone resection of non-invasive IPMN have increased risk (over baseline IPMN) of developing clinically significant remnant pancreatic lesions. The median 5-year risk is 10 % (range: 0−21 %). The purpose of postoperative surveillance in this setting is to proactively identify high-risk lesions to allow timely potentially curative intervention before the development of IC.	2+	C
CQ3-2	What is an appropriate interval, duration, and modality for postoperative surveillance after resection of IPMN?	Given the risk of clinically significant remnant pancreatic lesions, continuous surveillance is recommended as long as the patient remains fit to undergo additional therapeutic intervention. While the optimal surveillance protocol remains controversial and partly determined by resource availability, we recommend yearly imaging surveillance for patients without additional risk factors. For patients with a family history of pancreatic cancer or HGD, we recommend imaging surveillance every 6 months.	2+	C
CQ3-3	What imaging features during surveillance are predictive of HGD/IC of IPMN in the remnant pancreas?	Solid component, MPD dilatation, and growth of cystic lesion are imaging features that are predictive of HGD/IC of IPMN in the remnant pancreas. The development of MPD dilatation during surveillance should be carefully examined to determine whether it occurs by progression of main duct IPMN (MD-IPMN) or by other reasons including pancreato-enteric anastomotic stenosis	2+	D
CQ3-4	What factors increase the risk of developing clinically significant remnant pancreatic lesions after resection of non-invasive IPMN?	HGD and family history of pancreatic cancer are high risk features associated with the development of remnant pancreatic lesions during surveillance following resection of non-invasive IPMN. Patients with these characteristics should undergo strict imaging surveillance	2+	C
Pathological aspects (CQ4)				
CQ4-1	When referring to "HGD", can the terms "carcinoma in situ" and/or "malignant IPMN" be used?	"Carcinoma in situ" can be used as a synonym of HGD in IPMNs. Use of the term "malignant IPMN" is discouraged due to lack of clarity.	−	−
CQ4-2	What is the utility of IPMN morphological subtype for prognosis and assessment of recurrence risk?	The IPMN morphological subtype is associated with patient prognosis and adds to the prognostic information provided by grade of dysplasia. Low-grade gastric IPMNs are ancestors of co-occurring high-grade components, suggesting that low-grade gastric IPMNs cannot be disregarded as no-risk.	2+	C
CQ4-3	Should intraductal oncocytic papillary neoplasm (IOPN) be separated as a distinct entity from IPMN?	IOPN is a morphologically, molecularly, and clinically distinct neoplasm and should be separated from IPMN	2+	C
CQ4-4	What is the utility of molecular analysis of IPMN tissue for diagnosis, treatment, and surveillance?	Mutations in *KRAS* and *GNAS* (the most common mutations) are not reliably associated with prognosis of resected IPMNs. More data are needed on the association of other mutations with prognosis, particularly to distinguish the	2+	C

(*continued on next page*)

Table 1 (*continued*)

	Clinical questions	Recommendations	Evidence level[a]	Grade[a]
		added value of mutations to grade of dysplasia for prognostication with resected tissue. Genetic studies have underscored the multifocality and polyclonality of IPMNs, suggesting it may be a disease of the entire pancreas.		
CQ4-5	How should carcinoma associated with IPMN versus concomitant with IPMN be distinguished in clinical practice?	Clinical and pathological features accurately distinguish IPMNs with associated vs concomitant carcinomas in most cases. Concordant or discordant genetic alterations may be useful to make this distinction in challenging cases in clinical practice. Mimickers of IPMN may co-occur with pancreatic ductal adenocarcinoma and should be distinguished pathologically from true IPMNs.	2+	C
CQ4-6	What is the role of intraoperative frozen section diagnosis of IPMN in guiding additional surgical management?	Low grade dysplasia (LGD) at margin does not justify completion pancreatectomy. Additional resection if HGD or IC at the margin warrants clinical consideration. Denuded ducts at margin should not be interpreted as negative. In evaluation of the primary neoplasm, HGD and IC are often grossly indistinguishable from LGD, and thus cannot be excluded on a representative frozen section.	2+	C
CQ4-7	How should the current T staging system be implemented in carcinoma occurring with IPMN?	The size of the invasive component should be measured and reported separately from the IPMN. Microscopic measurement (cm) is recommended.	–	–
CQ4-8	What is the role of cytological evaluation of pancreatic cysts in preoperative risk stratification?	Preoperative evaluation/diagnosis of IPMN by cytology adds value to risk assessment and clinical management of patients with pancreatic cysts. Standardized reporting for cytology of pancreatic cysts is important for clinical management.	2+	C
Molecular markers in cystic fluid (CQ5)				
CQ5-1	Can cyst fluid molecular markers differentiate IPMN/mucinous cystic neoplasm (MCN) from other types of cysts?	Molecular markers including *KRAS*, *GNAS*, and v*HL*, can be used when the diagnosis of a pancreatic cyst is unclear and will alter surveillance.	1+	B
CQ5-2	Can cyst fluid molecular markers distinguish IPMN/MCN with LGD from HGD/IC?	*TP53*, *SMAD4*, *CDKN2A* and *PIK3CA* mutations are useful in identifying the presence of HGD and IC.	1+	B

[a] Evidence level and grade of recommendation according to Scottish Intercollegiate Guidelines Network (SIGN) 2019 [11].

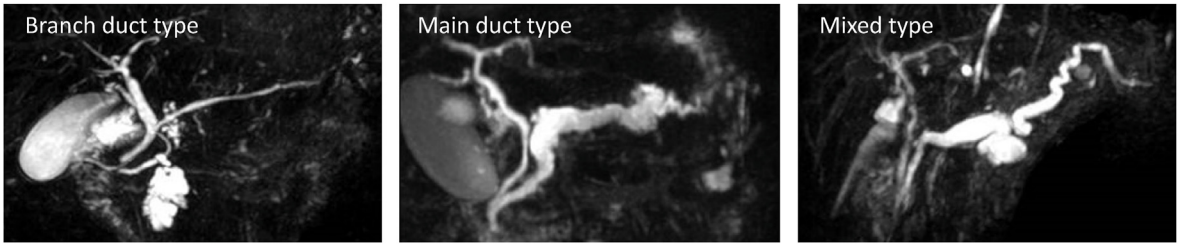


Fig. 1. Classification of IPMN on MRCP.
Left; branch duct type. Middle; main duct type. Right; mixed type. Reuse with permission from the Japanese Society of Gastroenterological Surgery [19].

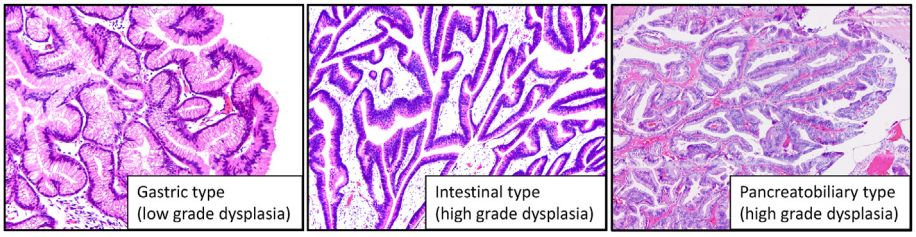


Fig. 2. Morphological findings of IPMN.
Left; gastric type with low grade dysplasia. Middle; intestinal type with high grade dysplasia. Right; pancreatobiliary type with high grade dysplasia. (x20, Hematoxylin and eosin staining).

neoplastic progression [26–28]. The subtype is also associated with pathological types of IC of IPMN; intestinal-type IPMNs are mostly associated with colloid carcinoma, while gastric-type and pancreatobiliary-type IPMNs are mostly associated with tubular ductal adenocarcinoma. The colloid carcinoma is prognostically more favorable than the ordinary PDAC [29–31]. Moreover, the subtype is associated with a risk for the development of HGD or IC in the remnant pancreas [7]. Therefore, the IPMN subtype provides additional discriminant information useful for management of patients beyond grade of dysplasia **(CQ4-2).** The previously described oncocytic subtype IPMN has recently been separated from IPMN as intraductal oncocytic papillary neoplasm (IOPN) because of recurrently found fusion genes involving *PRKACA* and *PRKACB* in this neoplasm **(CQ4-3)** [32,33]. Some studies showed that these IPMN subtypes and IOPN can be assessed preoperatively in biopsy samples including pancreatic juice cytology and cyst fluid analysis, enabling preoperative risk stratification [7]. Gastric subtype is the most frequent subtype and mostly a low-grade neoplasm [24], and most BD-IPMNs are of indolent gastric subtype. However, notably, recent molecular studies have uncovered that gastric subtype lesions are considered as an ancestor of co-occurring high-grade lesions including pancreatobiliary and

intestinal subtype lesions with HGD or IC, which indicates that the gastric subtype with LGD cannot be disregarded as no-risk **(CQ4-2)** [34]. If there are several subtypes in the same lesion, the subtype should be determined as that of the highest grade of dysplasia [27,35].

4.3. Genetic alterations and differential diagnosis

Identification of genetic alterations in resected specimens is helpful in the differential diagnosis of IPMN from other lesions, rather than to predict prognosis or to alter treatment **(CQ4-4)**. The frequent mutations in IPMN are *KRAS* (60–70 %) [36], *GNAS* (50–70 %) [37], and *RNF43*(15 %) [38]. Like the major 4 gene mutations in an ordinary PDAC, *KRAS* mutation is a founder mutation, and *TP53*, *CDKN2A*, or *SMAD4* mutation are progressor mutations in IPMN [39,40]. *KRAS* mutation at codon 12 is frequently observed in mucinous pancreatic cystic lesions such as IPMN [36] and mucinous cystic neoplasm (MCN) (40–67 %) [41–43], while rarely observed in other cystic lesions. *GNAS* mutation at codon 201 is exclusively observed in IPMN [37], and assessment of *GNAS* mutation is useful to discriminate IPMN from MCN.

PDAC may arise in being derived from or concomitant with IPMN. Definitions of the derived carcinoma and the concomitant PDAC were proposed by the Japan Pancreas Society, mainly regarding the topological relationship and histological transition between IPMN and the invasive component [44,45]. When PDAC originates in the vicinity of an IPMN, the distinction between these conditions is often difficult. In such situations, assessments of concordant or discordant molecular alterations including immunohistochemical features are helpful for the distinction **(CQ4-5)** [46]. Of note, combination of intestinal IPMN and colloid carcinoma can be determined as derived from IPMN, because concomitant PDAC exclusively shows tubular carcinoma. PDAC concomitant with IPMN have been reported to have a better prognosis than patients with PDAC without IPMN [3]; however, some of this difference is lost when adjusting for tumor stage, suggesting that the difference in survival is due to earlier detection of PDAC with earlier diagnosis of IPMN [12].

In resected specimens, mimickers of IPMN such as MCN [1,2], intraductal tubulopapillary neoplasm (ITPN) [24,47], retention cyst, and large duct type PDAC should be distinguished pathologically from IPMN **(CQ4-5)** [48]. Differential points from IPMN are the ovarian type stroma in MCN, no mucin secretion nor MUC5AC expression in ITPN, flat columnar cells in lining epithelia and upstream obstruction in the retention cyst, and invasive dilated ducts without ductal contour in the large duct type PDAC [7].

4.4. T-stage

The size of invasive component should be measured and reported separately from IPMN, because this factor is strongly associated with patients' prognosis **(CQ4-7)** [49]. The Verona consensus [25] recommended not to use the term "minimally invasive, and instead sub-staging of T1 (1a, b, c; $\leq$0.5 cm, >0.5 cm and $\leq$ 1 cm, > 1 cm) should be documented. However, few reports have followed this to date, and the clinical meaning especially for T1 subgroup staging must be validated in the future. Unique T stage of IPMN with IC remains a challenge.

5. Investigations

5.1. Diagnostic work-up

The patients with suspicion of having IPMN should be further assessed by physical examination, blood examination, cross-sectional imaging, and, if necessary, endoscopy with or without cytological assessments. Table 2 shows the typical clinical and imaging features of common pancreatic cysts which should be discriminated from BD-IPMN [3]. The vast majority of patients with small BD-IPMN are asymptomatic, while some patients have IPMN-related symptoms such as abdominal distention/pain, back pain (related to pancreatitis), jaundice, etc. Blood examinations include blood cell counts and the serum levels of transaminases, bilirubin, biliary enzymes, and pancreatic enzymes. Elevated levels of tumor markers and unexpected new onset or deterioration of diabetes mellitus (DM) often suggest the possible presence of IC, and carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and hemoglobin A1c (HbA1c) should also be assessed.

Primary cross sectional imaging modalities for the assessment of IPMN include contrast-enhanced magnetic resonance imaging/cholangiopancreatography (MRI/MRCP), and contrast-enhanced multi-detector computed tomography (MDCT) (Fig. 3). EUS can be used for further investigation to detect findings of HGD/IC, and contrast enhancement increases its diagnostic abilities **(CQ1-6)** (Fig. 4).

In the literature, MDCT, MRI, and EUS are equivalent in diagnosing IPMN with HGD/IC [6]. Even with recent improvement of imaging modalities, accuracy of diagnosis of pancreatic cystic lesions including IPMN and prediction of HGD/IC are 47–78 % and 73–97 %, respectively [50]. MRI and EUS are preferable in terms of avoiding the risk of radiation exposure, however MRI cannot be frequently performed in some regions because of high cost and the diagnostic ability of EUS is highly operator-dependent.

Diagnostic sensitivity of cyst fluid cytology obtained by EUS-FNA is low (overall 28.7 %, ranging 4.8–61.5 %) [51]; however, a positive result strongly influences management. Assessment of cystic fluid collected by EUS-FNA might also be helpful to confirm the presence of mucin or other indicators of a mucin-producing tumor, such as an elevated CEA or mutations associated with IPMN. The potential concern of peritoneal dissemination due to leakage of cyst fluid into the abdominal cavity or needle tract seeding in cases with carcinoma with EUS-FNA limits its use in some parts of the world. The incidence of needle tract seeding in pancreatic cystic lesion is reported to be 0.3 % by a systematic review [52]. On the other hand, when focusing on surgical cases of IPMN, the incidence of peritoneal seeding in preoperative EUS-FNA group was 2.3 %, and all IPMNs with peritoneal seeding were pathologically proven to be HGD/IC in resected specimen, although the incidence was not statistically different from that in non-preoperative EUS-FNA group (4.4%, p=0.403) [53]. In addition, there are large geographical variations in the use of EUS-FNA, and in general, it should be performed when further management will be altered according to the results. Taken together, EUS-FNA to obtain cytological and molecular marker assessment remains an option, and should not be performed when HRS is obvious in MDCT/MRI, and therefore surgery will be done regardless of the result.

The utility of endoscopic retrograde cholangiopancreatography (ERCP) during investigation of IPMN is limited to endoscopic biliary drainage for jaundiced patients. Routine ERCP to collect pancreatic juice for cytology is not recommended because of low sensitivity to diagnose HGD/IC (10–50 %) [54–56] and the possibility of post-ERCP pancreatitis. In patients with MD- and mixed IPMN, pancreatoscopy is sometimes useful to determine the adequate resection line, although it can lead to overdiagnosis, and the finding of a low-papillary lesion in the MPD can represent LGD [57–59]. There is not much information on the utility of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT to discriminate between HGD/IC and LGD; a few studies have described a sensitivity of 62–82 % and a specificity of 71–100 %, when the maximum of standardized uptake value is set at 1.3 to 3.0 [60–62].

Table 2
Typical clinical and imaging features of common pancreatic cysts.

Characteristics	BD-IPMN	MCN	SCN	Pseudocyst
Sex (% female)	~55 %	>95 %	~70 %	<25 %
Age (decade)	6th, 7th	4th, 5th	6th, 7th	4th, 5th
Asymptomatic	mostly when small	~50 %	~50 %	nearly zero
Location (% body/tail)	30 %	95 %	50 %	65 %
Common capsule	no	yes	yes	N/A
Internal structure	cyst by cyst	cyst in cyst	microcystic and/or macrocystic	unilocular
Gross appearance	grape-like	orange-like	spongy or honeycomb-like	variable
Calcification	no	rare, curvilinear in the cyst wall	30–40 %, central	no
Multifocality	20–40 %	no	no	rare
MPD	normal, or dilated to >5 mm suggesting mixed type	normal or deviated	normal or deviated	normal or irregularly dilated, may contain stones
MPD communication	yes	20 %	no	common
Cyst fluid analysis	mucin, high CEA, *KRAS* mutated, *GNAS* mutated	mucin, high CEA, *KRAS* mutated, *GNAS* wild	serous, very low CEA, *vHL* mutated, *KRAS*/*GNAS* wild	non-mucinous, high amylase, CEA can be elevated

Abbreviations: BD-IPMN, branch duct intraductal papillary mucinous neoplasm, MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; N/A, not applicable; MPD, main pancreatic duct; CEA, carcinoembryonic antigen. Reuse with permission from Elsevier (No. 5532990700460) [3].

5.2. Assessment of the risk and indication for operation

The factors predictive of HGD/IC in IPMN have been called HRS and WF since the 2012 guidelines [2]. HRS are very strong predictors of HGD/IC but do not have perfect specificity. The guidelines recommend careful decision of operative indication based not only on the degree of suspicion of HGD/IC, but also on the patients' general condition, comorbidity, life expectancy, and preference. Thus, the current guidelines continue to use the term "HRS" and "WF", instead of "absolute indication" and "relative indication" for surgery [10]. The management algorithm for IPMN is present in Fig. 3. This is designed for all IPMNs, including MD-IPMN [3].

5.3. High risk stigmata

The HRS are (1) obstructive jaundice in a patient with cystic lesion of the head of the pancreas, (2) an enhancing mural nodule ≥ 5 mm or solid component, (3) main pancreatic duct ≥10 mm, and (4) suspicious or positive results of cytology (if it was performed) (Fig. 3). Obstructive jaundice is a rare symptom in patients with IPMN, but if present, is a strong predictor of HGD/IC, with a sensitivity of 75 %–83 %, and a specificity of 61–65 % [63–65]. Even in benign IPMN with obstructive jaundice, an operation is usually required to relief symptoms and to avoid progression to HGD/IC. A mural nodule is a protruding lesion of the cystic wall and usually indicates a non-invasive lesion, while a solid component is a mass in the pancreatic parenchyma and indicates the possible presence of IPMN with IC or concomitant PDAC. In practice, it is sometimes difficult to distinguish mural nodule and solid component **(CQ1-1)**. The size of a mural nodule is usually measured by "height" of the nodule in EUS, and not "width" or "maximal diameter" [66], whereas by MDCT/MRI it is measured as maximal diameter. The cut-off value of the size of a mural nodule to diagnose HGD/IC remains controversial. Although enhancing mural nodule ≥ 5 mm has been accepted as a good cut-off value, with a sensitivity of 73–100 % and a specificity of 73–85 %, as described in the previous consensus guidelines 2017 [3] and European guidelines 2018 [10], it should be noted that the presence of mural nodule alone does not always have high impact on the prediction of HGD/IC, with an odd ratio of 1.19–3.16 in recent studies that have created nomograms [65–68]. Among these studies, one analysis using findings by EUS demonstrates that a cut-off value of ≥10 mm for the height of a mural nodule is more sensitive to predict HGD/IC (Odds ratio (OR) of 7.90 and 67 % of probability), when compared to a nodule between 5 and 10 mm (OR of 2.93 and less than 19 % probability). This controversy also applies to the cut-of value of MPD size. A MPD ≥10 mm alone does not have high impact on the prediction of HGD/IC (OR of 1.06–1.76) [66–68]. There was discussion regarding potential revision of enhancing mural nodule ≥10 mm as HRS, and any size of MPD dilation ≥ 5 mm as WF. However, because of lack of evidence strongly supporting these revisions, enhancing mural nodule ≥ 5 mm and MPD ≥10 mm have been left as HRS **(CQ1-2, CQ1-3)**, and enhancing mural nodule < 5 mm and MPD ≥ 5 mm and <10 mm as WF, which is the same as in the previous 2017 guidelines [3]. Cytological grade according to the World Health Organization (WHO) definition **[**24**]** demonstrates that the absolute risk of HGD/IC of "suspicious" and "positive" results are 91–100 % and 100 %, respectively [69,70], and therefore, "suspicious" and "positive" results are included as HRS **(CQ4-8)**.

5.4. Worrisome features

WF are (1) acute pancreatitis, (2) increased serum level of CA19-9, (3) new onset or acute exacerbation of DM within the past year, (4) cyst ≥30 mm, (5) enhancing mural nodule < 5 mm, (6) thickened/enhancing cyst walls, (7) MPD ≥ 5 mm and <10 mm, (8) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, (9) lymphadenopathy, and (10) cystic growth rate ≥2.5 mm/year [6]. These factors are almost the same as in the previous version [3], except for new onset or recent exacerbation of DM and cyst growth rate.

Around 20 % of the patients with IPMN who undergo resection have a history of acute pancreatitis. Most of these are patients have had a single episode that was mild and managed conservatively. Although there are several reports showing that acute pancreatitis is more frequently observed in IPMN with HGD/IC [71,72], larger series have shown that the incidence of IPMN with HGD/IC in patients with acute pancreatitis is same with that of LGD [68,73]. The main mechanisms of the occurrence of acute pancreatitis in patients with IPMN is MPD obstruction due to highly viscous mucin secretion, or MPD stenosis due to tumor involvement. Beyond the grade of dysplasia of IPMN, the presence of acute pancreatitis often deteriorates patient's daily life, and therefore, an operation should be considered in patients with repeated episodes of acute pancreatitis.

Elevation of CA19-9 (>37U/L) is a good predictor for various gastrointestinal cancers including PDAC, and for IPMN with IC, it

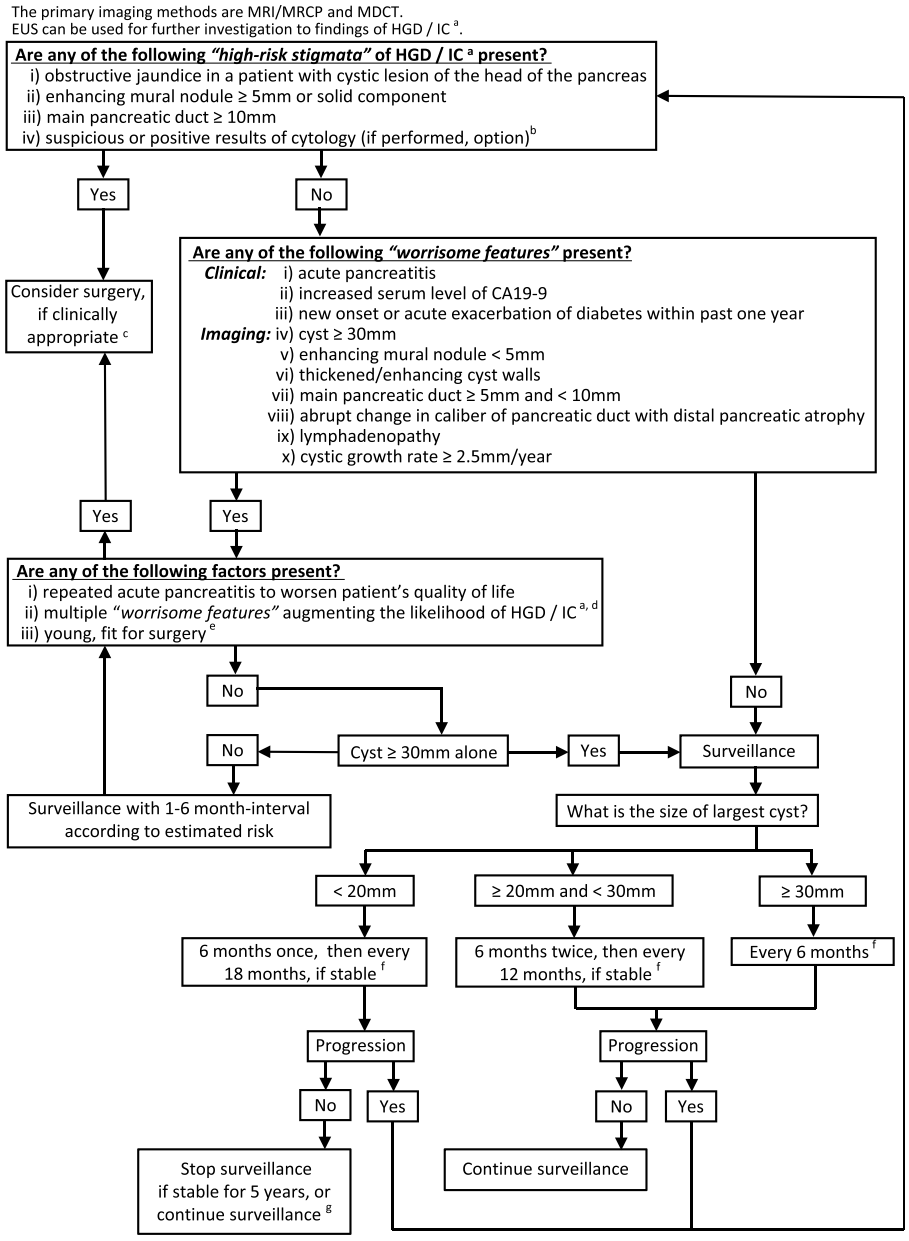


Fig. 3. Algorithm for the management of suspected BD-IPMN.
a. HGD; high-grade dysplasia, IC; invasive carcinoma. b. "Positive result" indicates "high-grade dysplasia" or "adenocarcinoma". c. See Fig. 5 showing operative principles and post operative surveillance. d. Nomogram can be referred. e. It is hard to define these ambiguous factors, and will be determined according to the physicians' viewpoints, patients' age, condition, life expectancy, and preference, cyst location, etc. f. Use combination of multi-detector computed tomography, magnetic resonance imaging/cholangiopancreatography, and endoscopic ultrasound, and blood examination including tumor marker/HbA1c, according to the institutional policy. g. Necessity of long-term surveillance remains unclear, and will be determined based on regional health economics, risk of concomitant ductal adenocarcinoma, and patients' age, condition, life expectancy, and preference, etc.

has a sensitivity of 41 %–74 % and a specificity of 85 %–96 % [66,74–76]. Recent reports have revealed that new onset DM is frequent (25 %) in IPMN patients, and carries an increased risk of HGD (risk ratio 1.27) and IC (risk ratio 1.61) [77–81]. Although definitions of "new onset" and "acute exacerbation" of DM have not been not yet been determined, they are included as WF in the current guidelines [4].

Thickened/enhancing cyst wall is an ambiguous factor, and measurement methods and cut-off value predictive of HGD/IC have not been established yet, but one report [82] has shown the odds ratio to predict HGD/IC is 3.51 when septal thickness is determined as ≥ 2.5 mm by EUS, which is comparable to the OR of 3.36 with a mural nodule size of ≥ 5 mm. Abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy [83,84] and lymphadenopathy [83,85] have been left as WF in the current guidelines according to the accumulated evidence, although this evidence is not of high level. More recent studies have demonstrated that cystic growth rate of IPMN as a predictor for progression to HGD/IC ranges from ≥0.96 mm to ≥3.5 mm/year, and the rate of ≥2.5 mm/year has been reported most frequently [86–89]. Thus, this rate is used as WF in the current guidelines instead of ≥ 5 mm/2 years of the previous version **(CQ1-4)**. "Increase in size of MPD" is also expected

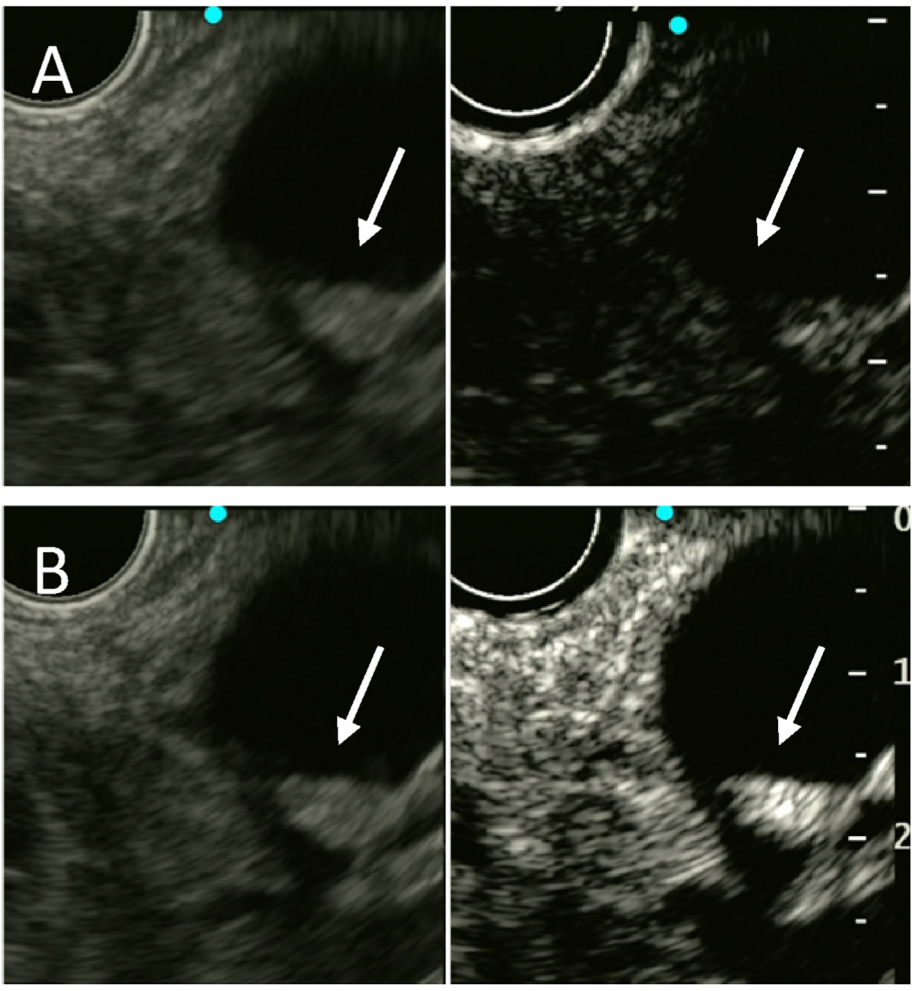


Fig. 4. Mural nodule detected by endoscopic ultrasound.
A. Finding before sonazoid injection. Arrow indicates mural nodule. B. Contrast-enhanced finding after sonazoid injection. Enhanced mural nodule (arrow) can be detected.

to predict an aggressive behavior of IPMN [4]; however, the evidence is lacking in this dynamic state issue, and this factor is not included as WF at this time.

5.5. Multiple WF

Presence of multiple WF has an additive effect on the risk of HGD/IC [90]. Zelga et al. [91] reported that the risk of HGD/IC increases in a stepwise fashion with the number of WF, to 22 %, 34 %, and 59 % with 1, 2, and 3 WF, respectively, and reached 100 % in patients with 4 or more WF. To improve the decision-making process of the candidate for operation or surveillance in IPMN patients, several reports have created nomograms which provide a graphical representation of a complex statistical formula and can provide a quantitative individualized risk score **(CQ2-4)**. The reported value of the area under the curve predictive of HGD/IC ranges from 0.739 to 0.955 [5,65–68,92–97]. Nomograms are a promising tool to manage patients with IPMN, but at present have some limitations, including lack of distinction between BD- and MD-IPMN in some of the models, small numbers of resected IPMNs in some countries or regions, and lack of external validation. If nomograms are used, an indication for an operation should be determined carefully by use of the most fit nomogram in each region/institution, and by discussing with patients based on their general condition, comorbidity, life expectancy, and preference **(CQ1-5)**.

6. Investigations of molecular markers in liquid biopsy samples

6.1. Serum

Except for CA19-9, there are no reliable markers in serum to predict the presence of HGD/IC. Investigations using serum microRNA or circulating cell-free DNA are now ongoing, and two reports [98,99] assessed cell-free DNA of IPMN patients and detected *GNAS* mutation in 32 % and 72 %, while *KRAS* mutation in 6 % and 0 % of IPMN patients.

6.2. Cyst fluid

Cyst fluid is considered as a good liquid biopsy sample for various pancreatic cysts including IPMN, and genetic profiling of cyst fluid is reported to reflect that of the cystic neoplasm well. The main purposes of the molecular assessment of cyst fluid are to discriminate mucinous cysts (IPMN, IOPN, ITPN, and MCN, which are precursors for HGD/IC and thus require resection or surveillance) from other cysts, and to distinguish between LGD and HGD/IC. Sensitivities and specificities to diagnose mucinous cyst using markers in cyst fluid are 79 % and 98 % by mutations in *KRAS* and/or *GNAS*, 58 % and 87 % by CEA (cutoff value > 192 ng/mL), and 93 % and 89 % by glucose (cutoff value < 50 ng/dL), respectively. **(CQ5-1)**

[8,100–103]. Traditionally, CEA in cyst fluid is frequently assessed, but up to 30 % of IPMNs have low levels, and it does not distinguish IPMN from MCN, and the concentration has no correlation with the grade of dysplasia. Assessment of mutations for *TP53, SMAD4, CDKN2A*, and *PIK3CA* may also be helpful in identifying the presence of HGD/IC, with low sensitivity (9–39 %) but high specificity (92–98 %) **(CQ5-2)** [8]. *VHL* mutation with neither *KRAS* nor *GNAS* is associated with >99 % sensitivity for a serous cystic neoplasm **(CQ5-1)** [8,100–103]. Taken together, assessment of molecular markers in cyst fluid will be helpful to plan the management of pancreatic cystic lesions including IPMN, while the indication of cystic fluid sampling by EUS-FNA is limited to when further management will be altered according to the results as described earlier in diagnostic work-up.

6.3. Resection for IPMN

Operative strategy for IPMN follows the prior guidelines from 2017 [3,104], and the principles for surgical resection are presented in Fig. 5.

BD-IPMN can usually be completely removed by partial pancreatectomy. Radical pancreatectomy with lymph node dissection should be performed when IC is suspected, while organ-preserving pancreatectomy without lymphadenectomy, such as middle pancreatectomy or spleen-preserving distal pancreatectomy, can be selected when the suspicion for IC is low based on the preoperative features and intraoperative findings. Minimally invasive approaches such as laparoscopic or robotic pancreatectomy can be utilized as well. Intraoperative frozen section is recommended to rule out unexpected MPD involvement at cut margin by neoplastic cells, even though macroscopic resection is completed.

During surgery for MD-IPMN and mixed IPMN, indication for radical pancreatectomy or organ-preserving pancreatectomy is same with BD-IPMN based on the degree of suspicious of IC as described above, while extension along the MPD is a concern, and the goal should be to obtain a negative surgical margin. If the results of intraoperative frozen section at cut margin show presence of IC or HGD, then additional resection is recommended **(CQ4-6)** [3,105–108]. If the results indicate normal epithelium or the presence of LGD, additional resection is unnecessary **(CQ4-6)** [108,109]. There have been many studies assessing impact of LGD at margin on risk of post-operative recurrence, but the results are very mixed [7,105–111]. Therefore, the systematic review group [7] concluded that there was insufficient data to recommend resection of additional tissue when only LGD is present at the margin **(CQ4-6)**. Of notes, post-operative recurrence is frequently an independent neoplasm from the one resected, and the LGD at the margin is often unrelated to the resected IPMN [6,7]. In addition, small IPMNs are often knowingly left behind in the remnant pancreas [6,7]. On the other hand, others have argued that the presence of HGD in the margin does not always mandate further resection when there is already invasive cancer in the resected pancreas, since the prognosis is dictated by the invasive component [109,111]. Therefore, leaving HGD at the margin may be appropriate to avid a total pancreatectomy in these cases, particularly in older or frail patients. We should also keep in mind that in colloid-type HGD/IC at the margin, there is a much lower rate of progression and a much higher curability, while tubular-type PDAC at the margin has a much faster rate of progression and a lower likelihood of cure [8,110,111]. Absence of epithelial cells at the transection margin (i.e. a denuded duct) is not equivalent to a negative margin, and if possible, an additional resection should be considered. **(CQ4-6)**. There are often difficult cases to obtain a negative surgical margin. Proximal pancreatectomy has an advantage technically for easiness of an additional resection when the margin is positive in intraoperative frozen section, while distal pancreatectomy is less invasive, and is also advantageous in terms of postoperative nutrition due to preservation of the duodenum, a main source of gastrointestinal hormones, but can limit obtention of further margins if the transection was done at the neck of the gland. Due to its endocrine and exocrine metabolic consequences, prophylactic total pancreatectomy is not recommended [112], however, possibility of total

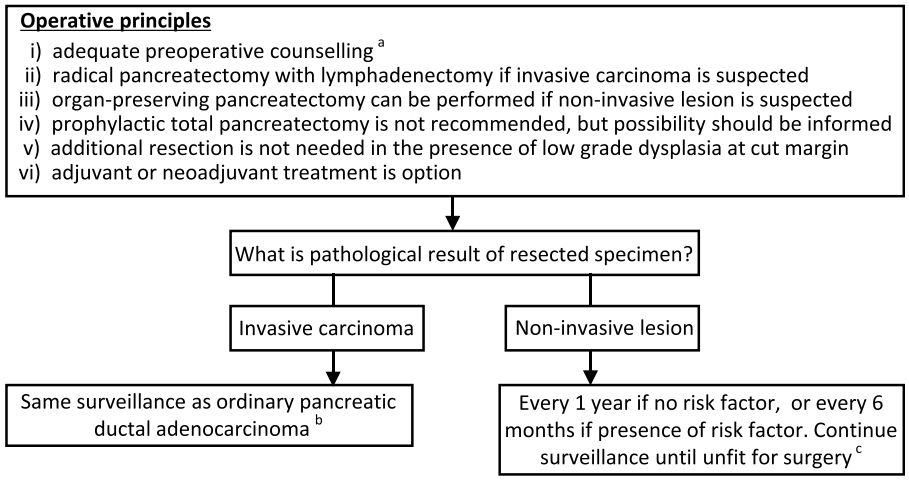


Fig. 5. Operative principles and postoperative surveillance for IPMN.
a. Following issues specific to IPMN should be informed to all patients at preoperative counselling in addition to usual perioperative events; (1) surgeons are usually going to make surgical choices in the operating room without knowing what the final diagnosis will be, (2) the resection might be extended up to the point of a total pancreatectomy if the operative findings show presence of high grade dysplasia/invasive cancer in the margins, (3) low grade dysplasia at cut margin or small indolent branch duct IPMN might be left in the remnant pancreas during partial pancreatectomy, and (4) long-term postoperative surveillance is needed even after partial pancreatectomy for low grade dysplasia with negative surgical margin because of unique characteristics of IPMN such as multifocality and skip progression. b. Follow the most fit protocol which is frequently used in each country/region. c. Pay attention to remnant pancreas for the possible development of clinically significant remnant pancreatic lesions, and risk factors for them are pathological result of high-grade dysplasia and the presence of family history of pancreatic cancer (**CQ3-4**). Use combination of physical examination, imaging study (multi-detector computed tomography, magnetic resonance imaging/cholangiopancreatography, and endoscopic ultrasound), and blood examination including tumor marker/HbA1c, according to the institutional policy. In patients undergoing total pancreatectomy for non-invasive lesion, IPMN-specific surveillance can be stopped if uneventful during 5-year postoperative surveillance.

pancreatectomy should be informed to all patients. Indication of total pancreatectomy should also be determined based on economic and social factors, because there are countries with limited economic, especially insulin availability. Some reports [113,114] have shown that intraoperative pancreatoscopy is potentially useful to determine the adequate resection line, however its accuracy to identify HGD/IC may be limited, and this technique has risk of peritoneal dissemination due to leakage of pancreatic juice containing neoplastic cells into the peritoneal cavity. If deemed necessary, pancreatoscopy should be performed preoperatively, although as described earlier this is not recommended as routine examination [57–59].

At preoperative counselling, following issues specific to IPMN should be informed to all patients in addition to usual perioperative events; (1) surgeons are usually going to make surgical choices in the operating room without knowing what the final diagnosis will be, (2) the resection might be extended up to the point of a total pancreatectomy if the operative findings show presence of HGD/IC in the margins, (3) LGD at cut margin or small indolent BD-IPMN might be left in the remnant pancreas during partial pancreatectomy, and (4) long-term postoperative surveillance is needed even after operation for LGD with negative surgical margin as described later.

6.4. Surveillance for non-resected IPMN

The cumulative incidence of transformation of indolent BD-IPMN to HGD/IC increases year-by-year, and is estimated to be 0.94–3.3 % by 5-years, 2.3–6.6 % by 10 years, and 7.6–15.0 % at 15-years. This transformation occurs more frequently in IPMN with larger cyst size or larger MPD diameter at the time of the initial diagnosis [115–117]. Recent pooled data analysis [5,118] have shown that the incidence of progression of BD-IPMN varies with the initial size at the time of diagnosis. For BD-IPMN <10 mm, the progression to WF is 4.8 % at a median of 54 months, for lesions between 10 and 20 mm, it is 10 % at 55 months, and for BD-IPMN between 20 and 30 mm, 48.8 % at a median of 23 months. **(CQ2-1)**. Therefore, the current guidelines recommend the surveillance protocol of BD-IPMN based on the stratification of 3 different cyst size; (1) 6 months once, then every 18 months, if stable, for BD-IPMN <20 mm, (2) 6 months twice, then every 12 months, if stable, for lesions ≥20 mm and <30 mm, and (3) every 6 months for BD-IPMN ≥ 30mm (Fig. 3) **(CQ2-2)**.

One of the great concerns is the need for long-term surveillance of small unchanged BD-IPMN. Recent analyses [118,119] showed several candidates for discontinued surveillance such as unchanged BD-IPMN <20 mm during a 5 years period, or a stable cyst during 5-year surveillance in individuals 75 years or older with a cyst < 3 cm, or those older than 65 years with cyst size <1.5 cm. On the other hand, a study from Japan [117] identified 22 pancreatic carcinomas during surveillance of 732 patients with BD-IPMN <15 mm, and showed that the cumulative incidences of pancreatic carcinoma were 2.2 %, 4.6 %, and 7.4 % at 5, 10, and 15 years, respectively. Of note, 14 of the 22 lesions were concomitant PDACs and the remaining 8 were carcinomas derived from IPMN. This group advocated the necessity of long-term surveillance over 5 years even in small BD-IPMN. Most Japanese physicians agree with the low risk of small unchanged BD-IPMN to progress to HGD/IC, while have concerns regarding possible development of concomitant PDAC apart from BD-IPMN. Therefore, the current guidelines recommend the two options, “stop surveillance” or “continue surveillance”, for small unchanged BD-IPMN after 5 years surveillance, until more evidence can be obtained. This issue is particularly important given the very large number of individuals who are being diagnosed with asymptomatic small BD-IPMN. Life-long surveillance would lead to an enormous healthcare expenditure as well as a burden on patients as well as physicians. The candidates for discontinued surveillance are those with stable small cysts (<2 cm) without WF/HRS and that remain unchanged for a period of 5-years. Surveillance should also be discontinued for patients who are unfit for surgery or have a life expectancy of <10 years [5] **(CQ2-3)**.

MRI along with physical examination and assessment of tumor marker and new onset diabetes are the preferred ways to provide surveillance, and MDCT and EUS should be considered when changes are observed in the MRI. Imaging modalities can be modified by institutional policies. It is noted again that whether continue or to stop surveillance, especially in older patients, should be determined based on patients’ general condition, comorbidity, life expectancy, and preference.

6.5. Concomitant PDAC

“Dual carcinogenesis” is one of the key elements during management of IPMN; progression of IPMN from LGD to HGD/IC (adenoma-carcinoma sequence), and development of PDAC apart from IPMN in the same pancreas [120,121]. Since the first reports of PDAC concomitant with IPMN in 1997 [122,123], there have been increasing studies showing that the cumulative risk of concomitant PDAC increases year-by-year, the yearly incidence being 0.4–1.0 % [117,124–130]. The risk of concomitant PDAC in IPMN patients is about 3 to 5-fold higher than that of the age-matched population [117,121,131], and thus, IPMN is a risk factor for PDAC. Of note, the IPMNs in patients who develop concomitant PDAC are typically small BD-IPMNs (Fig. 6), and the risk continues even after 5-year surveillance period [117,129,130]. It should also be noted that most studies regarding PDAC concomitant with IPMN have come from Japan, whereas in other countries the risk of developing concomitant PDAC in a patient who has IPMN appears to be similar to that of the general population [115,116,119]. This discrepancy may be related to the method of pathological assessment of resected specimens (the entire resected pancreas is cut by 5 mm slices in Japan), and high consciousness for concomitant PDAC in Japanese physicians [121]. Of note, the Johns Hopkins University group [132] pointed out that 18 % of co-occurring IPMN and invasive component are molecularly independent, suggesting the possibility of concomitant PDAC. In addition, the Massachusetts General Hospital group [131] also showed that the ratio of development of IPMN-derived cancer/concomitant PDAC during surveillance of BD-IPMN was 4/1, with a 5-year incidence of 5.5 % and standardized incidence ratio of 18.8.

7. Management of multifocal IPMNs

Incidence of multifocal BD-IPMNs is reported to be around 20–40 % [1], and the majority of these lesions arise independently based on the “field defect theory”. Molecular assessments support this multifocal independency [133–135]. Many reports demonstrated that multifocality does not increase the risk of HGD/IC of IPMNs [117,136–138], and therefore, management of multifocal IPMNs will be determined by the lesions having the highest risk. If a lesion is considered to have indication for surgery, then resection only of the high-risk lesion should be attempted, and others should be left untreated to avoid prophylactic total pancreatectomy. When there is multifocal BD-IPMNs and there is no indication for surgery, surveillance should be performed according to the lesion that has the highest risk.

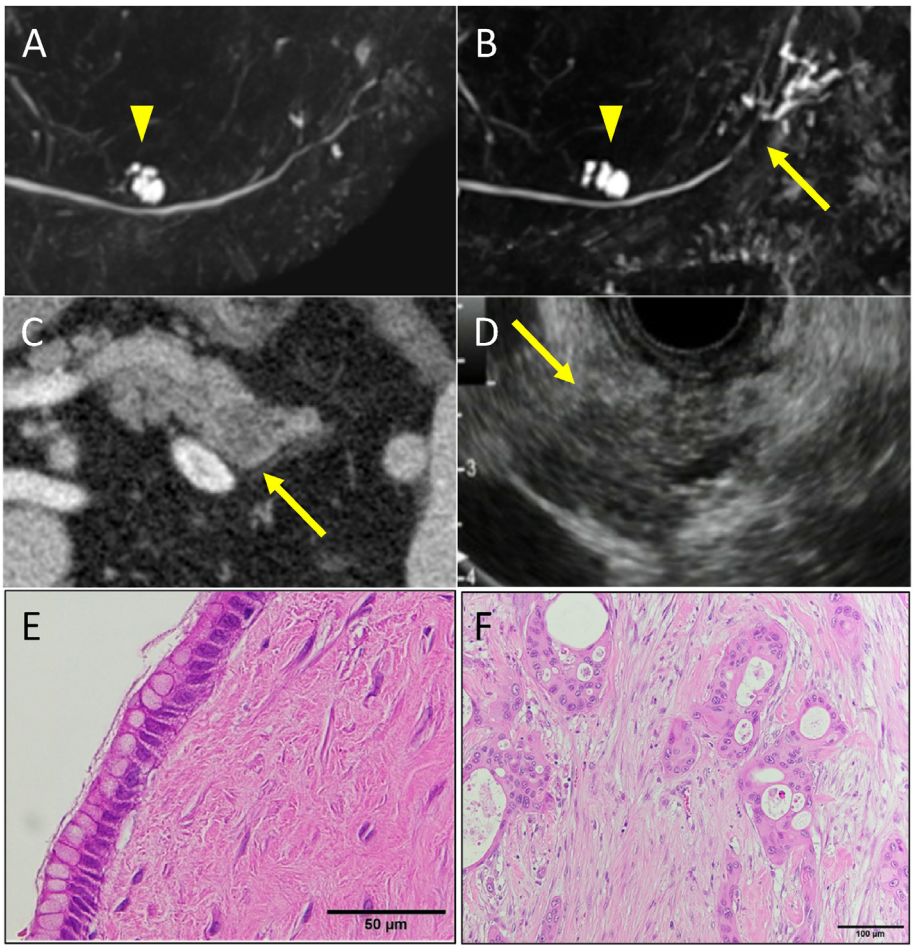


Fig. 6. Pancreatic ductal adenocarcinoma concomitant with BD-IPMN.
A. Magnetic resonance cholangiopancreatography (MRCP) shows 10 mm of BD-IPMN (arrow head) in the pancreas body. b. MRCP shows no change of BD-IPMN (arrow head) 14 months later, but stenosis of main pancreatic duct (MPD) (arrow) with distal dilation is noted. C. Computed tomography demonstrates a low-density solid lesion (arrow), 18 mm in diameter, in the pancreas tail. D. Endoscopic ultrasonography demonstrates a hypoechoic irregular solid lesion (arrow), 20 mm in diameter, in the pancreas tail. E. Distal pancreatectomy was performed. Pathological result of cystic lesion indicates low grade dysplasia of IPMN with gastric subtype. F. Pathological result of slid lesion indicates well to moderately differentiated tubular adenocarcinoma. There is neither topological communication nor transition area between cystic and solid lesions, and therefore, solid lesion is considered as pancreatic ductal adenocarcinoma concomitant with BD-IPMN.

8. Chemotherapy, radiotherapy, and ablation therapy for IPMN

The role of chemotherapy or radiotherapy for unresectable IPMN with IC and adjuvant/neoadjuvant treatment for resectable IPMN have not been established due to lack of high-quality evidence. In practice, most physicians use the regimens for ordinary PDAC [139]. Several reports [139–142] have shown that IPMN with node positive MUC2-negative tubular carcinoma will benefit from adjuvant chemotherapy. The effects of radiotherapy or chemo-radiotherapy for IPMN with IC in a palliative setting have not been clarified.

Several trials of ablation therapy using ethanol injection into pancreatic cystic lesions including IPMN with or without chemotherapeutic agents such as gemcitabine and paclitaxel have been reported [143–147]. The patients who are considered candidates for ablation therapy are those with contraindication for surgery but long-life expectancy, unilocular or oligo-locular mucinous cyst without definitive communication with MPD, and larger cysts without mural nodule [143]. The reported efficacy of ablation ranges from 9 to 72 %, with adverse events rate of 9–23 %, most frequent of which is pancreatitis [143–147]. Long-term results showing an oncological benefit are lacking, and because of this, ablation therapy for IPMN should only be done in the context of a clinical trial.

9. Surveillance after resection of IPMN

Distant metastatic recurrence in liver, peritoneum, lymph node, or lung is often observed after resection of IPMN with IC as seen after resection of ordinary PDAC, and overall survival of these two entities are equivalent when stage is aligned [29,44,148–151].

One of the unique characteristics of IPMN is that clinically significant lesions requiring resection might develop in the remnant pancreas even after margin-negative partial pancreatectomy for non-invasive IPMN, and thus, careful attention should also be paid to the remnant pancreas as well as extra-pancreatic organs during postoperative surveillance after partial pancreatectomy for IPMN **(CQ3-1)** [152–155]. There are three distinct mechanisms for development of lesions in the remnant pancreas; (1) new development of multifocal IPMN or progression of multifocal untreated IPMN in the remnant pancreas independent from the primary lesion [156], (2) recurrence of initially resected IPMN in the remnant pancreas such as local recurrence in margin-positive or

skip progression in margin-negative situation [157,158], and (3) development of PDAC concomitant with IPMN [159,160]. Only (2) is precisely real recurrence, while (1) and (3) are multifocal independent lesions, although it is often difficult to discriminate these two entities in daily practice. These lesions include various benign and malignant lesions, and if these lesions would be indication for resection, then, they are called as "clinically significant remnant pancreatic lesions" in the current guidelines.

The median cumulative 5-year incidence of clinically significant remnant pancreatic lesions is 10 % (range, 0–21 %) [152–156,158,161–167], and the risk continues to increase even after 5-years. The median incidence of all remnant pancreatic lesions, clinically significant remnant pancreatic lesions, and invasive remnant pancreatic lesions after partial pancreatectomy for non-invasive IPMN are 19 % (range, 8–28 %), 10 % (0–21 %), and 4 % (1–10 %), respectively **(CQ3-1)** [152–156,158,161–167]. The risk factors for the development of clinically significant remnant pancreatic lesions are having HGD in the pathology of the initial operation and the presence of family history of PDAC **(CQ3-4)** [156,168,169]. The presence of HGD is considered to be a marker of an aggressive phenotype of IPMN in which the whole pancreas is at increased risk of cancer development. In addition, HGD has an ability to disseminate in the whole pancreas via intraductal spread mechanism (skip progression) [112]. On the other hand, as described later, a family history of PDAC does not increase the likelihood of transformation of IPMN from LGD to HGD/IC [170,171], but is a predictor of metachronous development of concomitant PDAC.

Even after resection of LGD with a negative-margin, and no residual lesions, there is a risk of developing neoplastic lesions in the remaining parenchyma [6]. Therefore, all resected IPMNs are at a risk of metachronous development of clinically significant remnant pancreatic lesions, and such risk continues to increase after 5 years of the initial operation, and because of this post-operative surveillance should be continued until the patient is surgically unfit. In patients undergoing total pancreatectomy for non-invasive lesion, IPMN-specific surveillance can be stopped if uneventful during 5-year postoperative surveillance.

The imaging findings to predict the possible presence of clinically significant remnant pancreatic lesions are presence of solid mass, MPD dilation, and growth of the cyst **(CQ3-3)** [152,172,173]. It should be noted that after a pancreatoduodenectomy or a middle (or central) pancreatectomy, there can be a dilated MPD that is a result of stenosis of the pancreatic anastomosis, but also can be caused by neoplastic progression [174]. To detect clinically significant remnant pancreatic lesion in a timely fashion, MRI, MDCT, and/or EUS should be considered as described in surveillance of non-resected IPMN (Fig. 3). Regarding interval of surveillance, every 6-month for the patients with risk factor for clinically significant remnant pancreatic lesion and every 12-month for those without risk factors is recommended (Fig. 5). **(CQ3-2)** [6,175].

10. The effect of family history of pancreatic cancer

Family history of pancreatic cancer is defined as the presence of pancreatic cancer in one or more first-degree family members (parent, sibling, or child) by the Cancer of the Pancreas Screening (CAPS) study group [176,177], a definition that has been used worldwide. This definition is different from familial pancreatic cancer defined as the presence of germline mutations such as *ATM*, *BRCA1/2*, *MLH1*, and *CDKN2A* [178,179]. These two entities should be clearly discriminated when used.

The CAPS study group demonstrated that 20 % of the individuals with the high-risk for pancreatic lesions have IPMNs, indicating that there exists a possible association between the development of IPMN and a family history of pancreatic cancer [180–182]. In addition, other groups have shown that the incidence of PDAC concomitant with IPMN is higher in patients with family history of pancreatic cancer than those without [170,171]. They also suggested that the family history of pancreatic cancer does not increase the risk of t progression of IPMN from LGD to HGD/IC [170,171]. Therefore, more attention should be paid to the possible occurrence of concomitant PDAC during management of IPMN in patients with family history of pancreatic cancer.

11. Extra-pancreatic neoplasms

The patients with IPMN frequently have extra-pancreatic neoplasms, the reported incidence ranging from 20 to 30 % [1]. The distribution of the involved extra-pancreatic organs differs among races and counties; skin, breast, kidney, and prostate are frequent in the western countries, while gastro-intestine in Asian. In 80 % of IPMN patients with extra-pancreatic neoplasm, IPMNs are found during initial assessment of or during surveillance after resection of extra-pancreatic neoplasms, and in the remaining 20 %, extra-pancreatic neoplasms are diagnosed during surveillance of IPMN [183–185].

IPMN tends to develop in elderly patients. Advancement of health screening system leads to frequent diagnosis of IPMN, and it has been reported that the incidence of extra-pancreatic neoplasm in patients with IPMN is comparable to that of the population-based incidence of each country [186–188]. Therefore, no additional screening for extra-pancreatic neoplasms is necessary for patients who have IPMN.

Acknowledgements

The authors thank Prof. Masao Tanaka for his special remarks during the 26th meeting of IAP and providing crucial advice for the preparation of the manuscript, and Prof. Yoshifumi Takeyama and Prof. Kyoichi Takaori for their special supports to the international meeting during IAP in Kyoto 2022. This study was supported by Grant-in-Aid for Scientific Research (KAKEN) (22K19567 and 23H02984).

The authors also thank Alberto Balduzzi, Hironari Kato, Mamoru Takenaka, Shin Haba (Revision of HRS/WF), Sayada Zartasha Kazmi, Hye-Sol Jung, Youngmin Han, Won-Gun Yun, Young Jae Cho, Mirang Lee, Wooil Kwon, Marco Del Chiaro, Giovanni Marchegiani, Brian Kim Poh Goh, Shounak Majumder, Yosuke Nakai, Aesun Shin (Surveillance of non-resected IPMN), Camilo Correa-Gallego, Yuto Hozaka,; Hitoe Nishino, Makoto Kawamoto, Dorice L. Vieira (Surveillance after resection of IPMN), Volkan Adsay, Olca Basturk, Lodewijk A.A. Brosens, Noriyoshi Fukushima, Seung-Mo Hong, Sung-Joo Kim, Jae W. Lee, Claudio Luchini, Michaël Noë, Martha B. Pitman, Aldo Scarpa, Aatur D. Singhi, Mariko Tanaka (Pathological aspects), and Michael Johannes Pflüger, Kevin Tony Jamouss, Elham Afghan, Su Jin Lim, Salvador Rodriguez Franco, Harrison Mayo, Marcus Spann, Hao Wang, Aatur Singhi (Molecular markers in cyst fluid), for their special contributions to systematic reviews.

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