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Review article

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

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ABSTRACT

The international consensus guidelines for management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasm of the pancreas established in 2006 have increased awareness and improved the management of these entities. During the subsequent 5 years, a considerable amount of information has been added to the literature. Based on a consensus symposium held during the 14th meeting of the International Association of Pancreatology in Fukuoka, Japan, in 2010, the working group has generated new guidelines. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. To simplify the entire guidelines, we have adopted a statement format that differs from the 2006 guidelines, although the headings are similar to the previous guidelines, i.e., classification, investigation, indications for and methods of resection and other treatments, histological aspects, and methods of follow-up. The present guidelines include recent information and recommendations based on our current understanding, and highlight issues that remain controversial and areas where further research is required.

1. Introduction

Since the publication of the international consensus guidelines for management of intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) of the pancreas in 2006 [1], these entities have been drawing increasing attention. As a consequence, a considerable amount of information has been added to the literature during the subsequent 5 years. In particular, new information has been obtained regarding endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the cyst contents, the indications for resection of branch duct IPMN (BD-IPMN) have changed from rather early resection to more deliberate observation, and some reports have documented the occurrence of concomitant pancreatic ductal adenocarcinoma (PDAC) in patients with BD-IPMN. All this new knowledge makes an update of the guidelines imperative. During the 14th meeting of the International Association of Pancreatology (IAP) held in Fukuoka, Japan, in 2010, we arranged a symposium where recent progress in preoperative diagnosis and management was presented. All the speakers in the symposium, including eight initial members and six

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new members of the working group, have generated new guidelines based on an elaborate list of items to be addressed. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. We have made a series of recommendations for all items in Table 1. However, since the grades of the recommendations are low, we have avoided repetition of grade C in almost all of the items.

All the authors contributed equally to the guidelines. M. Tanaka chaired and C. Fernandez-del Castillo co-chaired this working group of the IAP, and these two authors played a major role in the preparation of the manuscript. The remaining authors are listed in alphabetical order.

Table 1
Summary of recommendations.

1. Classification
   1a. The threshold of MPD dilation, segmental or diffuse, for characterization of MD-IPMN has been lowered to >5 mm without other causes of obstruction, thereby increasing the sensitivity for radiologic diagnosis without losing specificity. MPD dilation of 5–9 mm is considered a "*worrisome feature*", while an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*".
   1b. The definition of "malignancy" of IPMNs and MCNs has been variable, hampering comparisons of data. We recommend abandoning the term carcinoma in situ in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification.

2. Investigation
   2a. CT or MRI with MRCP is recommended for a cyst of ≥1 cm to check for "*high-risk stigmata*", including enhanced solid component and MPD size of ≥10 mm, or "*worrisome features*", including cyst of ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy. All cysts with "*worrisome features*" and cysts of >3 cm without "*worrisome features*" should undergo EUS, and all cysts with "*high-risk stigmata*" should be resected. If no "*worrisome features*" are present, no further initial work-up is recommended, although surveillance is still required.
   2b. MDCT and MRCP are most useful for distinguishing BD-IPMN from other cysts by showing multiplicity and a connection to the MPD.
   2c. Cyst fluid analysis is still investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" in centers with expertise in EUS-FNA and cytological interpretation.
   2d. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.
   2e. Distinction of BD-IPMN from a small oligocystic SCN is challenging and may require EUS-FNA with cyst fluid CEA determination.

3. Indications for Resection
   3a. Resection is recommended in all surgically fit patients with MD-IPMN. If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia.
   3b. The indications for resection of BD-IPMN are more conservative. "*Worrisome features*" as well as "*high-risk stigmata*" are proposed. A BD-IPMN of >3 cm without "*high-risk stigmata*" can be observed without immediate resection.
   3c. Surgical resection is recommended for all surgically fit patients with MCN. For MCNs of <4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation should be considered.

4. Methods of Resection and Other Treatments
   4a. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs. Focal non-anatomic resections or anatomic resections without lymphadenectomy or splenectomy may be considered for those without suspicion of malignancy, but carry a risk of possible leakage of mucin, and higher incidences of pancreatic fistulae and recurrence. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery.
   4b. EUS-guided ethanol ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.
   4c. Multifocal BD-IPMNs carry a similar risk of malignancy to unifocal BD-IPMN. Segmental resection can be performed to remove the IPMNs at the highest oncological risk. The threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC and multifocal BD-IPMNs, but the data supporting this idea are incomplete.

Table 1 (*continued*)

5. Histological Aspects
   5a. The type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should be part of the reporting of IPMNs, with colloid carcinomas being characterized by "intestinal" differentiation and a better prognosis than tubular carcinomas.
   5b. Instead of "minimally invasive carcinoma" derived from IPMN or MCN, it would be more appropriate to stage invasive carcinomas with the conventional staging protocols and further substage the T1 category into T1a (≤0.5 cm), T1b (>0.5 cm and ≤1 cm), and T1c (1–2 cm).
   5c. The histologic subtypes of IPMN have clinicopathologic significance. The gastric type is typically low grade, with only a small percentage developing into carcinoma. However, if a carcinoma does develop, it is usually of the tubular type and aggressive. Large intestinal-type IPMNs can have invasive carcinoma of the colloid type with indolent behavior.
   5d. If clear high-grade dysplasia or invasive carcinoma is present at the margin by frozen section analysis, further resection is warranted. All patients should be informed preoperatively about the possibility of total pancreatectomy. Moderate-grade or low-grade dysplasia may not require any further therapy.
   5e. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN, being careful to identify the MPD as precisely as possible when processing the specimen.
   5f. A distinction between PDAC derived from an IPMN and PDAC concomitant with an IPMN is proposed with regard to the topological relationship and histological transition, although the distinction sometimes remains undetermined.

6. Methods of follow-up
   6a. Patients without "*high-risk stigmata*" should undergo MRI/MRCP (or CT) after a short interval (3–6 months) to establish the stability, and then annual history/physical examination, MRI/MRCP (or CT) and serologic marker surveillance. Short interval surveillance (3–9 months) should be considered for patients whose IPMN progresses toward "*high-risk stigmata*" and patients with a family history of hereditary PDAC. Some investigators continue surveillance at short intervals owing to concern over the development of distinct PDAC.
   6b. Non-invasive MCNs require no surveillance after resection. IPMNs need surveillance based on the resection margin status. If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable. The aspect of whether a margin with moderate-grade dysplasia increases recurrence is unknown. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice a year. The follow-up strategy of invasive IPMN should be identical to that for PDAC.
   6c. In patients with two or more affected first-degree relatives, the risk rapidly escalates and merits aggressive surveillance by MRI/MRCP (or CT) and EUS. "*Worrisome features*" are of more concern. If present, patients should be considered for resection if they are surgically fit. If absent, patients should be followed by MRI/MRCP (or CT) at 3-month intervals and EUS annually for the first 2 years. Patients with a rapidly growing BD-IPMN and patients who develop "*worrisome features*" should be strongly considered for resection. The interval of surveillance after 2 years of no change can be lengthened to 6 months, but no longer in view of the relatively high incidence of PDAC reported for BD-IPMN.
   6d. There are no screening recommendations for detecting extrapancreatic malignancies in patients with IPMN on surveillance and after resection, but consideration of extrapancreatic neoplasms should be made based on the frequency of these malignancies in the general population of the country or region.

2. Classification

2.1. Criteria for distinction of BD-IPMN and main duct IPMN (MD-IPMN)

IPMNs can be classified into three types, i.e., MD-IPMN, BD-IPMN, and mixed type, based on imaging studies and/or the histology (Fig. 1) [1]. MD-IPMN is characterized by segmental or diffuse dilation of the main pancreatic duct (MPD) of >5 mm without other causes of obstruction. According to recent reports, a low threshold for MPD dilation (5 mm) can be adopted, which increases the sensitivity for radiologic diagnosis of MD-IPMN without losing specificity [2–10]. In the revised guidelines, MPD

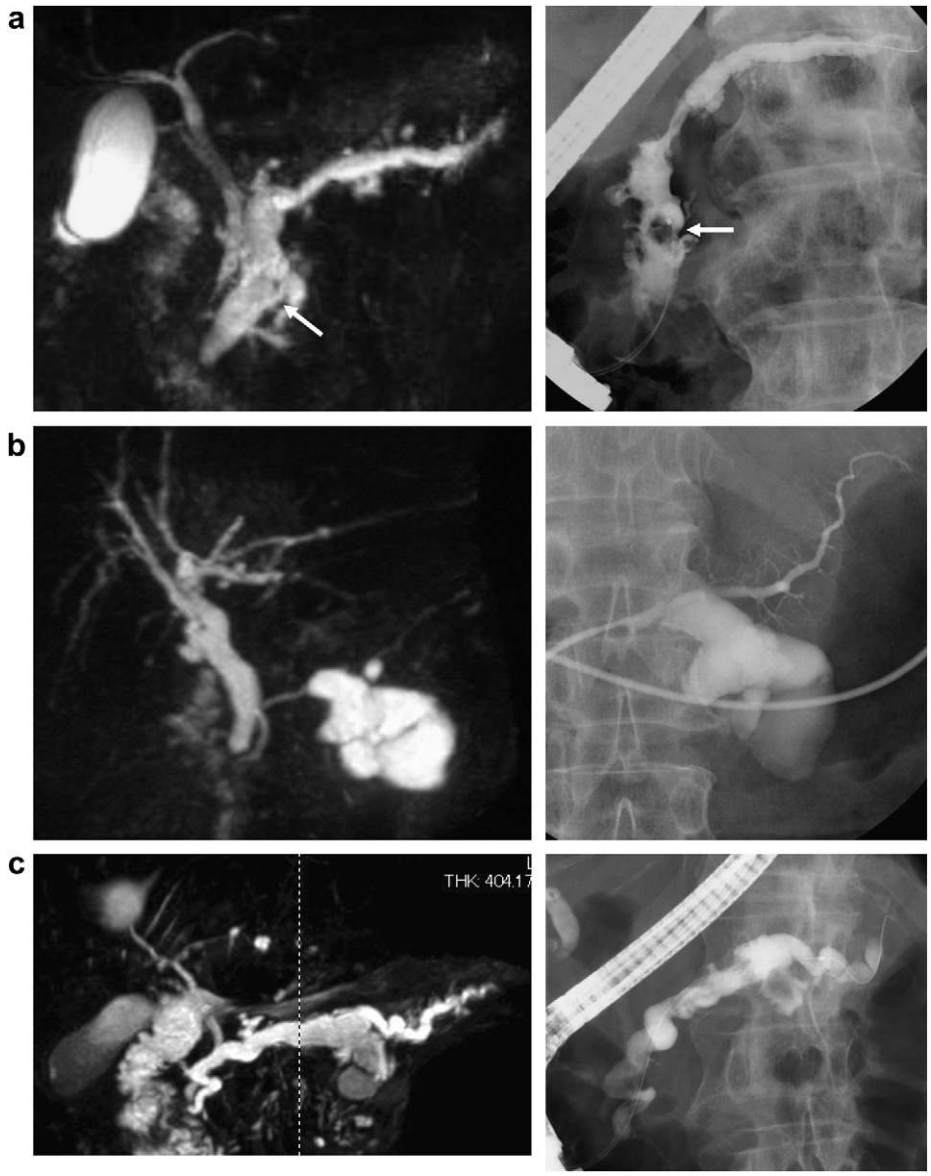


Fig. 1. MRCP (left panels) and ERCP (right panels) demonstrating the three morphological types of IPMN. a. Main duct type with a mural nodule (arrows). b. Branch duct type. c. Mixed type.

dilation of 5–9 mm is considered a "*worrisome feature*" and an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*". Pancreatic cysts of >5 mm in diameter that communicate with the MPD should be considered as BD-IPMN, with pseudocyst being in the differential diagnosis for patients with a prior history of pancreatitis. Mixed type patients meet the criteria for both MD-IPMN and BD-IPMN.

There are considerable differences in the proportions of each type and the risks of malignancy (Table 2) [2–23]. The differences are partly caused by variation in the type definitions, since the correlation between the histologic and radiologic criteria is around 70% [8,24]. While the MPD can be dilated through ductal hypertension caused by mucin, protein plugs, and focal pancreatitis, neoplastic involvement without ductal dilation can be seen histologically [25]. Since the classification is important for clinicians to plan the management, it should be based on the preoperative radiologic images, and the pathological classification can be specified a posteriori.

2.2. Definition of malignant IPMN and MCN

IPMNs and MCNs exhibit a spectrum of neoplastic transformation, both within each category and often in a given case, ranging from innocuous lesions that used to be called "hyperplasia" or adenoma (currently classified as "low-grade dysplasia") to invasive carcinomas [26,27]. The definition of "malignancy" has been variable, with most authors including "carcinoma in situ" (CIS) in the malignant category, while others reserve this term for invasive neoplasms, and yet others define "malignancy" by aggressive clinical behavior [27]. This wide variation hampers comparisons of data, and hinders determination of the significance of lesions and placement of patients into clearly defined categories. For this reason, we recommend abandoning the term CIS in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification [26].

Table 2
Frequencies of malignancy in IPMNs according to the morphological types.

Total IPMNs					Main duct type			Branch duct type			Mixed type		
First author	Year	Total number	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)	Number *n* (%)	Malignant *n* (%)	Invasive *n* (%)
Sugiyama [11]	2003	62	34 (54.8%)	20 (32.3%)	30 (48.4%)	21 (70.0%)	17 (56.7%)	32 (51.6%)	13 (40.6%)	3 (9.4%)			
Sohn[a][12]	2004	136	>52 (38.2%)	52 (38.2%)	36 (26.5%)	>18 (50.0%)	18 (50.0%)	60 (44.1%)	>18 (30.0%)	18 (30.0%)	33 (24.3%)	>16 (48.5%)	16 (48.5%)
Salvia [13]	2004	140	83 (59.3%)	58 (41.4%)	140 (100%)	83 (59.3%)	58 (41.4%)						
Suzuki[a][14]	2004	1024	>446 (43.6%)	446 (43.6%)	201 (19.6%)	>120 (59.7%)	120 (59.7%)	509 (49.7%)	>150 (29.5%)	150 (29.5%)	228 (22.3%)	148 (64.9%)	148 (64.9%)
Lee [15]	2005	67	24 (35.8%)	9 (13.4%)	27 (40.3%)	12 (44.4%)	3 (11.1%)	35 (52.2%)	10 (28.6%)	4 (11.4%)	5 (7.5%)	2 (40.0%)	2 (40.0%)
Serikawa [2]	2006	103	41 (39.8%)	28 (27.2%)	47 (45.6%)	30 (63.8%)	21 (44.7%)	56 (54.4%)	11 (19.6%)	7 (12.5%)			
Schmidt [3]	2007	156	50 (32.1%)	29 (18.6%)	53 (34.0%)	30 (56.6%)	15 (28.3%)	103 (66.0%)	20 (19.4%)	14 (13.6%)			
Rodriguez [20]	2007	145	32 (22.1%)	16 (11.0%)				145 (100%)	32 (22.1%)	16 (11.0%)			
Schnelldorfer [16]	2008	208	82 (39.4%)	63 (30.3%)	76 (36.5%)	49 (64.5%)		84 (40.4%)	15 (17.9%)		48 (23.1%)	18 (37.5%)	
Kim [17]	2008	118	36 (30.5%)	28 (23.7%)	70 (59.3%)	25 (35.7%)	23 (32.9%)	48 (40.7%)	>3 (6.3%)	3 (6.3%)			
Nagai [4]	2008	72	44 (61.1%)	30 (41.7%)	15 (20.8%)	15 (100%)	10 (66.7%)	49 (68.1%)	25 (51.0%)	18 (36.7%)	8 (11.1%)	4 (50.0%)	2 (25.0%)
Jang [21]	2008	138	26 (18.8%)	17 (12.3%)				138 (100%)	26 (18.8%)	17 (12.3%)			
Ohno [18]	2009	87	45 (51.7%)	19 (21.8%)	14 (16.1%)	11 (78.6%)	4 (28.6%)	48 (55.2%)	20 (41.7%)	9 (18.8%)	25 (28.7%)	14 (56.0%)	6 (24.0%)
Nara [19]	2009	123	82 (66.7%)	61 (49.6%)	26 (21.1%)	26 (100%)	21 (80.8%)	59 (48.0%)	26 (44.1%)	14 (23.7%)	38 (30.9%)	30 (78.9%)	26 (68.4%)
Bournet [7]	2009	99	24 (24.2%)	14 (14.1%)				47 (47.5%)	6 (12.8%)	4 (8.5%)	52 (52.5%)	18 (34.6%)	10 (19.2%)
Hwang [5]	2010	187	58 (31.0%)	43 (23.0%)	28 (15.0%)	20 (71.4%)	17 (60.7%)	118 (63.1%)	19 (16.1%)	14 (11.9%)	41 (21.9%)	19 (46.3%)	12 (29.3%)
Mimura [6]	2010	82	54 (65.9%)	29 (35.4%)	39 (47.6%)	34 (87.2%)	19 (48.7%)	43 (52.4%)	20 (46.5%)	10 (23.3%)			
Sadakari [22]	2010	73	6 (8.2%)	1 (1.4%)				73 (100%)	6 (8.2%)	1 (1.4%)			
Kanno [23]	2010	159	40 (25.2%)	19 (11.9%)				159 (100%)	40 (25.2%)	19 (11.9%)			
Crippa [10]	2010	389	181 (46.5%)	118 (30.3%)	81 (20.8%)	55 (68%)	39 (48%)	159 (40.9%)	34 (22%)	17 (11%)	149 (38.3%)	92 (62%)	62 (42%)
Total		3568	>1440 (>40.4%)	1100 (30.8%)	883 (24.7%)	>549 (>62.2%)	385 (43.6%)	2027 (56.8%)	>494 (>24.4%)	337 (16.6%)	627 (17.6%)	>361 (>57.6%)	284 (45.3%)

Abbreviation: IPMN: intraductal papillary mucinous neoplasm.
[a] Since these reports only included invasive IPMNs, the frequency of malignant IPMNs is underestimated in this table owing to the absence of data for non-invasive IPMNs.

3. Investigation

3.1. Work-up for cystic lesions of the pancreas

Cystic lesions are increasingly being recognized by imaging studies, and the frequency of pancreatic cyst detection by MRI (19.9% [28]) is higher than by CT (1.2% [29] and 2.6% [30]). A cyst with invasive carcinoma is uncommon in patients with an asymptomatic pancreatic cyst, particularly one of <10 mm in size, and therefore no further work-up may be needed at that point, although follow-up is still recommended [31,32]. For cysts greater than 1 cm, pancreatic protocol CT or gadolinium-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) is recommended for better characterization of the lesion (Fig. 2) [33]. A recent consensus of radiologists suggested dedicated MRI as the procedure of choice for evaluating a pancreatic cyst, based on its superior contrast resolution that facilitates recognition of septae, nodules, and duct communications [33]. When patients are required to undergo frequent imaging for follow-up, MRI may be better for avoiding radiation exposure.

For amelioration of symptoms, and owing to the higher risk of malignancy, all symptomatic cysts should be further evaluated or resected as determined by the clinical circumstances.

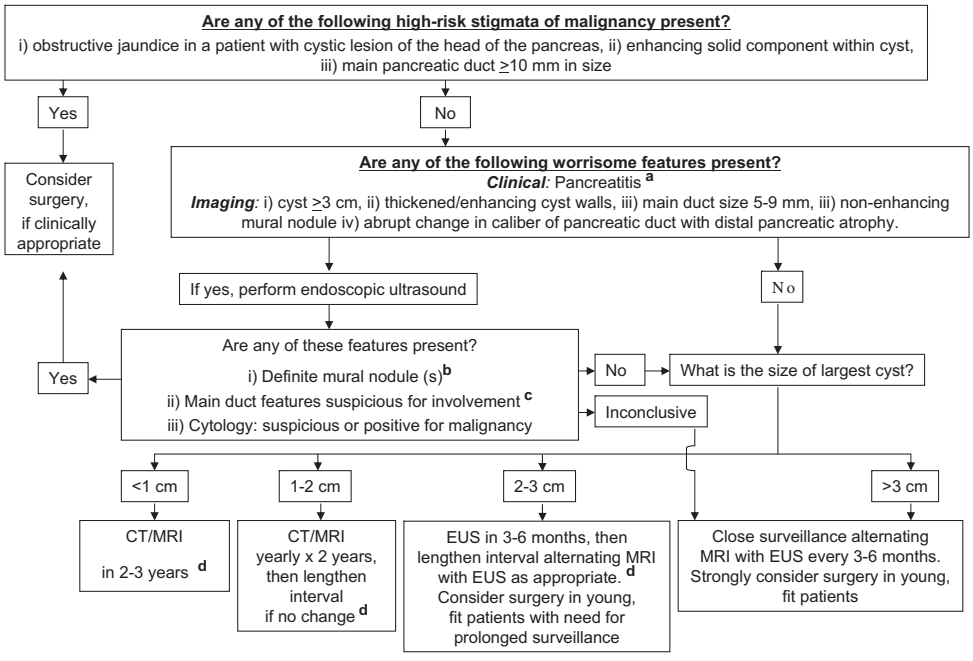
"*Worrisome features*" on imaging include cyst of ≥3 cm, thickened enhanced cyst walls, MPD size of 5–9 mm, non-enhanced mural nodules, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy [34–38].

Cysts with obvious "*high-risk stigmata*" on CT or MRI (i.e., obstructive jaundice in a patient with a cystic lesion of the pancreatic head, enhanced solid component, MPD size of ≥10 mm) should undergo resection without further testing. All smaller cysts with "*worrisome features*" should be evaluated by EUS to further risk-stratify the lesion. Patients with cysts of >3 cm and no "*worrisome features*" can also be considered for EUS to verify the absence of thickened walls or mural nodules, particularly if the patient is elderly.

All patients with cysts of ≤3 cm in size without "*worrisome features*" should undergo surveillance according the size stratification (Fig. 2) [39].

3.2. Distinction of BD-IPMN from MCN and other pancreatic cysts

Using a combination of the clinical history, sex, imaging characteristics, cytology, and cyst fluid and chemical analyses of carcinoembryonic antigen (CEA) and amylase, pancreatic cysts can not only be characterized as mucinous or non-mucinous, but also accurately identified for their specific subtypes [40–56]. A combination of the clinical and imaging characteristics provides the best initial preoperative diagnosis of the cyst type (Table 2). For an imaging diagnosis of BD-IPMN, multidetector CT (MDCT) and MRCP are the most useful primary methods for defining the morphology, location, multiplicity, and communication with the MPD. [8,9,18,57,58]. Reliable distinguishing features of BD-IPMN include multiplicity and visualization of a connection to the MPD, although such a connection is not always observed. EUS can then be used for detecting mural nodules and invasion, and is most effective for delineating the malignant characteristics (Fig. 3) [18], although it has the limitation of operator dependency [13,58]. Chemical



a. Pancreatitis may be an indication for surgery for relief of symptoms.
b. Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue
c. Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is incolclusive.
d. Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

Fig. 2. Algorithm for the management of suspected BD-IPMN.

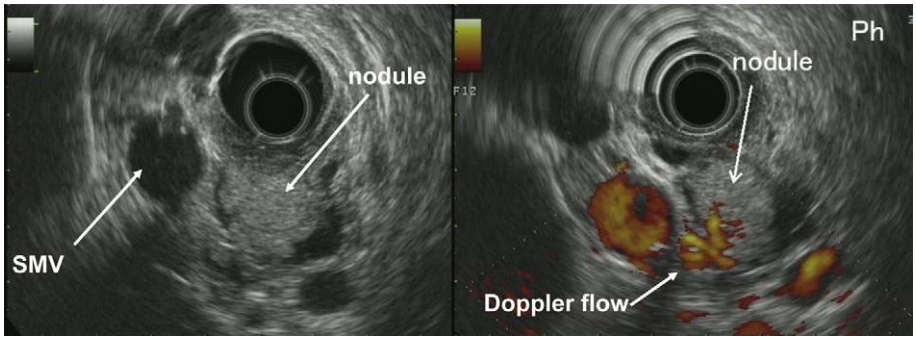


Fig. 3. EUS showing a mural nodule in the dilated MPD with Doppler flow indicating the presence of a blood supply.

analyses of the CEA and amylase levels as well as cytology of the cyst content obtained by EUS-FNA are often useful, but cannot distinguish MCN and IPMN [47,51,54–56]. A more recent study claimed that a molecular analysis for *GNAS* mutations can distinguish MCN from BD-IPMN [59].

3.3. Roles of cyst fluid analysis and cytology obtained by EUS-FNA in the diagnosis of cystic lesions of the pancreas

The use of EUS-FNA varies widely throughout the world. Elevated CEA is a marker that distinguishes mucinous from non-mucinous cysts, but not benign from malignant cysts [53–56,59–63]. A cut-off of ≥192–200 ng/ml is ~80% accurate for the diagnosis of a mucinous cyst [53–55]. An increase the cut-off value improves the specificity at the expense of the sensitivity [63]. A low CEA level does not exclude a mucinous cyst. Cyst fluid amylase is not uniformly elevated in IPMN, and MCN may also exhibit elevated amylase levels [53]. Serous cysts typically have low levels of both CEA and amylase. Cytology can be diagnostic, although the sensitivity is limited by the scant cellularity [50,51,63–71]. In summary, interpreting the results of biochemical markers in cyst fluid is a complex exercise in pattern recognition, and should be reserved for patients in whom additional information will have an impact on the surgical decision-making.

In centers with expertise in EUS-FNA and cytological interpretation, cytological analysis adds value, especially for evaluation of a small BD-IPMN without "*worrisome features*" [56]. "High-grade epithelial atypia" recognizes epithelial cells with cellular atypia that is qualitatively and quantitatively insufficient for a malignant interpretation, and may be a more sensitive predictor of malignancy than positive cytology [3,51,56,72,73]. Such cells in the cyst fluid predicted malignancy in a mucinous cyst with 72% sensitivity and positive predictive value (80% accuracy) in one study [51], and detected 30% more cancers in small IPMN than "*worrisome features*" in another study [56].

Molecular analyses of the cyst fluid for diagnosis are still evolving. Studies show that detection of *KRAS* mutations more accurately supports a mucinous rather than malignant cyst [45–47]. A recent study indicates that *GNAS* mutations may be helpful in distinguishing significant mucinous cysts from indolent cysts that can be conservatively managed [59].

It is important to highlight that Japanese investigators do not recommend cyst fluid analysis for the diagnosis of mucinous-like cystic lesions, and believe that a cyst of any size with "*worrisome features*" should not be aspirated, because it may cause leakage of the cyst content, possibly leading to peritoneal dissemination [74,75]. At present, EUS-FNA with cytological and molecular analyses is still considered investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" only in centers with expertise in EUS-FNA and cytological interpretation.

3.4. Role of cytology and/or analysis of the pancreatic juice in the diagnosis of malignant BD-IPMN

Pancreatic juice can be obtained via endoscopic retrograde cholangiopancreatography (ERCP) by washing or brushing for cytology. Pancreatic juice can also be obtained from the MPD or a dilated branch duct affected by IPMN, although selective cannulation may be difficult. Only a few reports mention pancreatic juice cytology of BD-IPMN, with variable yields [70,76]. One large series showed a significant role of CEA levels of >30 ng/ml in diagnosing malignant BD-IPMN [77]. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.

3.5. Distinction of BD-IPMN from serous cystic neoplasm (SCN)

Serous cystadenomas have three morphological patterns: polycystic, honeycomb, and oligocystic. BD-IPMN can be properly distinguished from SCN with a polycystic or honeycomb pattern by either CT or MRCP [55,74,78,79] (Table 3). The differentiation between a small oligocystic SCN and a BD-IPMN is challenging and may require EUS-FNA with cyst fluid CEA determination [80–82].

4. Indications for resection

4.1. Indications for resection of MD-IPMN

According to published series of ≥50 cases (Table 2), the mean frequency of malignancy in MD-IPMN is 61.6% (range, 36–100%) and the mean frequency of invasive IPMN is 43.1% (range, 11–81%) [2–6,11–19]. Considering these high incidences of malignant/invasive lesions and the low 5-year survival rates (31–54%) [3–5,12–14], surgical resection is strongly recommended for all surgically fit patients. However, MPD dilation of 5–9 mm should be considered as one of the "*worrisome features*", similar to the case for BD-IPMN (Fig. 2), with a recommendation of evaluation but no immediate resection. To date, there have been no consistent predictive factors for malignancy in MD-IPMN, including the degree of MPD dilation, presence of symptoms, or mural nodules [5,11,13].

The aim of resection is to achieve complete removal of a tumor with a negative margin. In the segmental ectatic type or diffuse type with focal lesions (mural nodules or combined branch lesions, etc.), it is relatively easy to determine the resection side (proximal or distal pancreatectomy) and transection line.

Table 3
Typical clinical and imaging features of common pancreatic cysts.

Characteristic	MCN	BD-IPMN	SCN	Pseudocyst
Sex (% female)	>95%	~55%	~70%	<25%
Age (decade)	4th, 5th	6th, 7th	6th, 7th	4th, 5th
Asymptomatic	~50%	Mostly when small	~50%	Nearly zero
Location (% body/tail)	95%	30%	50%	65%
Common capsule	Yes	No	Yes	N/A
Calcification	Rare, curvilinear in the cyst wall	No	30–40%, central	No
Gross appearance	Orange-like	Grape-like	Spongy or honeycomb-like	Variable
Multifocality	No	Yes	No	Rare
Internal structure	Cysts in cyst	Cyst by cyst	Microcystic and/or macrocystic	Unilocular
Main pancreatic duct communication	Infrequent	Yes (though not always demonstrable)	No	Common
Main pancreatic duct	Normal or deviated	Normal, or dilated to >5 mm, suggesting combined type	Normal or deviated	Normal or irregularly dilated, may contain stones

Abbreviations: MCN, mucinous cystic neoplasm; BD-IPMN, branch duct intraductal papillary mucinous neoplasm; SCN, serous cystic neoplasm; N/A, not applicable.

In the diffuse dilation type without focal lesions, more careful evaluation is warranted, including ERCP. Some of these patients may not even have IPMN, but rather chronic pancreatitis. A dilated papilla with mucin extrusion and/or a mural nodule visualized by ERCP definitely confirms the diagnosis of MD-IPMN. If indeed IPMN is diagnosed, right-sided pancreatectomy is preferred because it is technically easier to resect additional pancreatic tissue to achieve a negative margin.

Frozen biopsy sections are useful for deciding the resection line [83]. If the resection margin is positive for high-grade dysplasia, additional resection of the pancreas should be attempted to obtain a negative margin. If low-grade or moderate-grade dysplasia is found, further resection is controversial [84–87]. Total pancreatectomy should be applied selectively in younger patients who can handle the complexities of brittle diabetes and exocrine insufficiency [88,89]. Intraductal ultrasonography (Fig. 4), pancreatoscopy (Fig. 5), and cytology have been used to obtain additional information of the surgical margin in difficult cases [90,91]. However, all of these investigations should preferably be performed preoperatively to avoid leakage of mucin.

4.2. Indications for resection of BD-IPMN

The mean frequency of malignancy in resected BD-IPMN is 25.5% (range, 6.3–46.5%) and the mean frequency of invasive cancer is 17.7% (range, 1.4–36.7%) (Table 2) [2–7,11–23]. Although resection of BD-IPMN therefore warrants consideration, these lesions mostly occur in elderly patients, and the annual malignancy rate is only 2–3% [92,93]. These factors support conservative management with follow-up in patients who do not have risk factors predicting malignancy. The usefulness of the previous consensus criteria for resection [1] has been validated by many reports [5–8,22–24,94,95]. New high-risk factors proposed include a rapidly increasing cyst size [92,96] and high-grade atypia rather than “positive” cytology [51,56,65,67,72].

Although still controversial, younger patients (<65 years) with a cyst size of >2 cm may be candidates for resection owing to the cumulative risk of malignancy [21,97]. The decision needs to be individualized and to depend not only on the risk of malignancy but also on the patient’s conditions and cyst location. Since a BD-IPMN size of >3 cm is a weaker indicator of malignancy than the presence

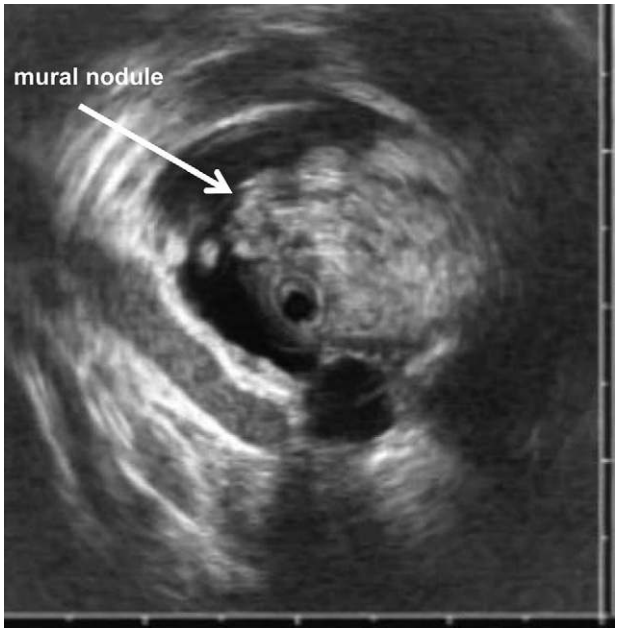


Fig. 4. Intraductal ultrasonogram demonstrating a 25-mm mural nodule in the MPD.

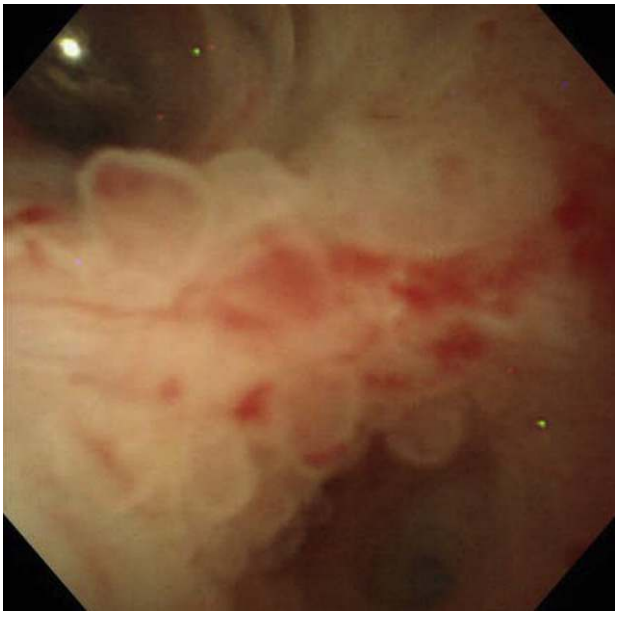


Fig. 5. Peroral pancreatoscopic photograph showing a fish egg-like mucosal lesion in the MPD.

of mural nodules and positive cytology, BD-IPMN of >3 cm without these signs can be observed without immediate resection, particularly in elderly patients.

4.3. Indications for resection of MCN

MCN defined by the presence of ovarian stroma has a low prevalence of invasive carcinoma (<15%) with no malignancy in MCNs of <4 cm without mural nodules [40,98]. Observation may be considered in elderly frail patients [40]. However, given the relatively young age of most patients, the risk of progression to invasive MCN, and their common locations in the pancreatic body and tail, surgical resection is recommended for all surgically fit patients, since the natural history of MCN is still unknown and nonoperative management would require years of follow-up based on high-resolution imaging associated with high costs [40,98–100]. Patients with invasive MCN are significantly older (by 11 years) than those with non-invasive MCN, [98–100], and frequently contain areas of low-grade dysplasia [40,98,99], suggesting that we are presently unable to securely identify invasive MCN. Resection is routinely curative in non-invasive MCN with no recurrence [40,98].

MCNs are usually located in the pancreatic body and tail, and thus require distal pancreatectomy that can be performed safely at high-volume centers [101,102]. In patients with MCNs of <4 cm without mural nodules, parenchyma-sparing resections (i.e. middle pancreatectomy) and distal pancreatectomy with spleen preservation as well as laparoscopic procedures should be considered [102,103].

5. Methods of resection and other treatments

5.1. Methods of pancreatectomy for invasive and non-invasive MCNs and IPMNs

Although preoperative and intraoperative assessment of the dysplasia grades of MCNs and IPMNs can be difficult, US, CT, MRI, and EUS will identify most tumors with a significant invasive component [104]. In such patients, pancreatoduodenectomy, left pancreatectomy, or total pancreatectomy according to the site and extent of the disease with lymph node dissection remains the standard treatment [105,106]. Limited resections or even focal non-anatomic resections (excision, enucleation, uncinatectomy) may be considered for MCN or BD-IPMN without clinical, radiologic, cytopathologic, or serologic suspicion of malignancy [107–124]. However, non-anatomic resections may be associated with rare, but possible, leakage of mucin followed by pseudomyxoma peritonei [125,126], and also have a higher incidence of pancreatic fistulae and risk of recurrence from potentially residual neoplasm. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery [127–129]. Conversion to a standard resection with lymphadenectomy should occur if intraoperative findings raise concern for malignancy or frozen-section pathology reveals high-grade dysplasia or invasive disease. When the final pathology reveals invasion or positive margin for high-grade dysplasia undetected on frozen sections, a reoperation should be performed in surgically fit patients.

5.2. Role of mucosal ablation by ethanol injection under EUS guidance in the management of MCN or IPMN

Investigators have begun exploring the possibility of EUS-guided ablation of pancreatic cysts by ethanol or ethanol followed by paclitaxel [130–132]. Preferred candidates include (1) patients with cystic lesions of >2 cm, either unilocular or oligolocular, that show no communication with the MPD, and (2) cysts in patients who refuse surgery or are high-risk surgical candidates [133,134]. The reported short-term CT-defined cyst resolution rates were 33–79% [131–135], and variable histopathologic degrees of epithelial ablation were observed in the resected specimens [131,133,135]. DeWitt et al. [134] reported that follow-up by CT revealed no evidence of cyst recurrence for a median of 26 months after cyst resolution. Complications include acute pancreatitis (4.5–10%), abdominal pain (<20%), and splenic vein obliteration [131,133,135].

Although the procedure may be promising, there are some problems that remain to be addressed, including insufficient ethanol infiltration and impossible imaging surveillance after the cyst collapse [129]. Moreover, recent studies have shown that PDAC occurs quite frequently not only as malignant transformation of IPMN but also in other sites separate from IPMN [39,136–138]. More research needs to be carried out on the techniques, materials, long-term outcomes, and adequacy of this procedure. At present, EUS-guided ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.

5.3. Approach to multifocal BD-IPMN

IPMN probably represents a pancreatic “field defect”, i.e., all pancreatic ductal epithelial cells are at risk of dysplastic change, and this can be apparent in patients with multifocal (two or more) BD-IPMNs (Fig. 6). Current series estimate that 25–41% of all BD-IPMNs are multifocal [3,8,20]. There is no convincing evidence that the risk of invasive IPMN multiplies according to the number of lesions. In fact, in one series, patients with symptomatic unifocal BD-IPMN carried a higher risk than those with symptomatic multifocal BD-IPMNs (18% versus 7%) [3].

The treatment approach to multifocal BD-IPMNs should mirror that of unifocal BD-IPMN. When resection is indicated, segmental anatomic pancreatectomy should be performed in cases where the multifocal disease is limited to a pancreatic region. In some cases, the disease may not be able to be eliminated without total pancreatectomy. Even then, it is reasonable to perform a segmental resection to remove the IPMNs at the highest oncological risk and perform surveillance of the remaining lesions. However, the threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC, because of the increased prevalence of higher-grade lesions [139].

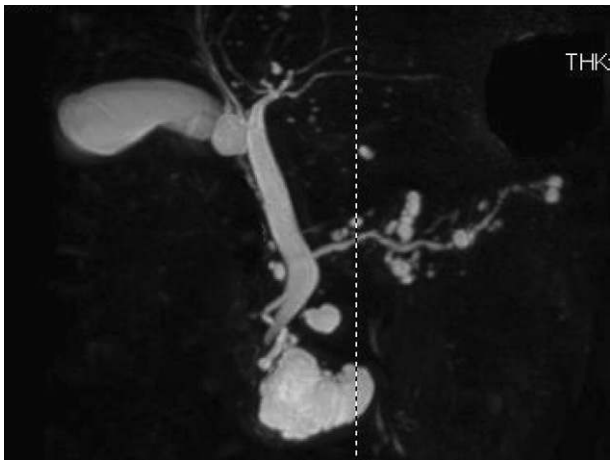


Fig. 6. MRCP demonstrating multifocal BD-IPMNs.

6. Histological aspects

6.1. Types of invasive carcinoma of malignant IPMN

It is now well established that the type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should therefore be part of the reporting of IPMNs [140–143]. Colloid carcinomas are characterized by "intestinal" differentiation, evidenced by diffuse and specific expression of CDX2 and MUC2, and have a better prognosis than tubular carcinomas [142]. It is conceivable that these histological differences may drive the use of distinct adjuvant chemotherapy protocols, although this has not yet been evaluated.

6.2. Pathologic definition of minimally invasive carcinoma derived from IPMN or MCN

6.2.1. Staging of invasive carcinomas (definition of "minimally invasive carcinoma")

Since the term "minimally invasive" has been variably defined by different authors [144–147], it is preferable to avoid such a non-specific term. Instead, it would be more appropriate to stage invasive carcinomas with conventional staging protocols including the AJCC/TNM [148], and then further substage the T1 category (those with invasive carcinomas of <2 cm) into T1a for those that are ≤ 0.5 cm, T1b for those that are >0.5 cm and ≤ 1 cm, and T1c for those that are 1–2 cm. This substaging of T1 conforms to the methods that are being employed for other organs and tumor types, allows the collection of more accurate and comparable data for future evaluation, and is in accordance with the recent proposal made by Furukawa et al. [149].

6.3. Distinction and clinical relevance of gastric, intestinal, pancreatobiliary, and oncocytic forms of IPMNs

The cell lineage of the "papillary component" of IPMNs has clinicopathologic significance (Fig. 7) [142,147,149–153]. The vast majority of BD-IPMNs are of the gastric type, which is MUC5AC-positive but MUC1-negative, with MUC2 highlighting only the scattered goblet cells. The gastric type is typically low grade, with only a small percentage developing into carcinoma, although if a carcinoma does develop in these patients, it is usually of the tubular type and behaves like a conventional PDAC [151,153]. A significant portion of MD-IPMNs are of the intestinal type, showing diffuse expression of CDX2 and MUC2. Large and complex intestinal-type IPMNs can have invasive carcinoma, typically of the colloid type (CDX2/MUC2-positive) and with relatively indolent behavior [142]. The oncocytic type is defined by complex arborizing papillae with delicate cores, oncocytic cells, and intraepithelial lumina formation, and common MUC6 expression [154,155]. This type tends to be large, with a more obscure intraductal nature and relatively uncommon and limited invasion, and most cases receive a clinical diagnosis of "cystadenocarcinoma" [156]. The pancreatobiliary type is the least well characterized and the least common, and is regarded by some as a high-grade version of the gastric type. Invasive carcinoma associated with this type is usually tubular and aggressive [150].

Based on the clinical associations described above, it is sometimes feasible to predict the subtypes preoperatively. In a preoperative biopsy, EUS-guided or otherwise, it may be possible to employ this subclassification, provided that the papillary component of the tumor is sampled. One study obtained consistent subclassifications in 15 of 19 patients (79%) by preoperative sampling of the pancreatic juice via endoscopy [157].

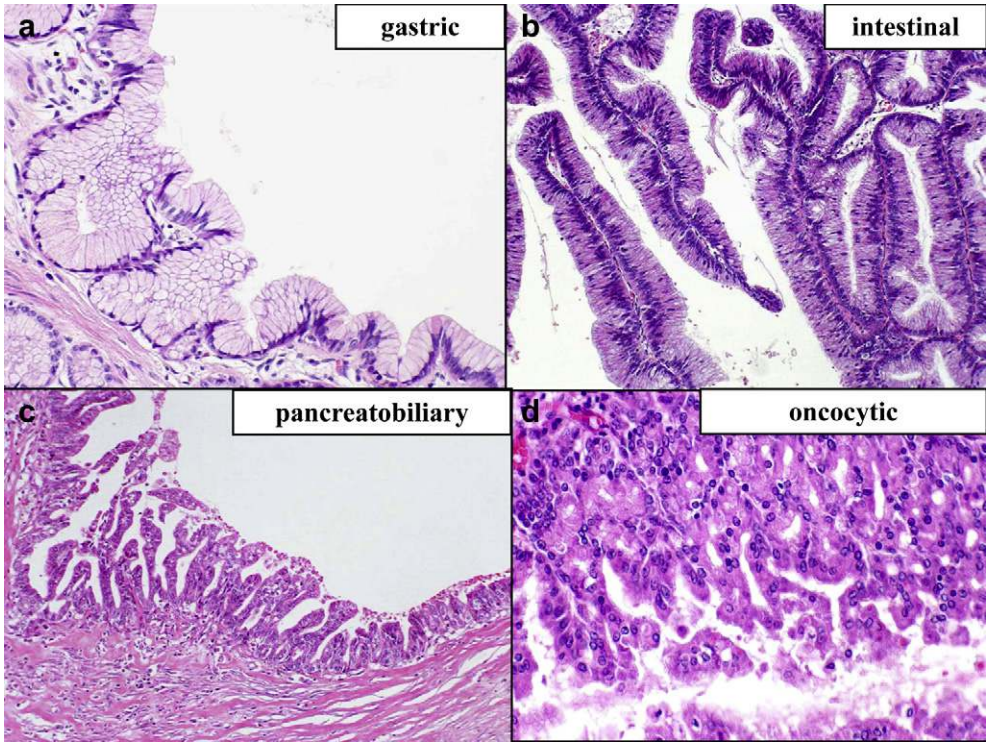


Fig. 7. Histological subclassification of IPMNs. a. The gastric type shows tall columnar cells with basally oriented nuclei and abundant pale mucinous cytoplasm. b. The intestinal type is composed of tall papillae lined by columnar cells with pseudostratified nuclei and basophilic cytoplasm with variable amounts of apical mucin. c. The pancreatobiliary type has thin branching papillae with high-grade dysplasia. The cells are cuboidal and have round hyperchromatic nuclei, prominent nucleoli, and moderately amphophilic cytoplasm with a less mucinous appearance. d. The oncocytic type usually exhibits complex arborizing papillae lined by two to five layers of cuboidal to columnar cells with large, round, fairly uniform nuclei containing single, prominent, eccentrically located nucleoli, and abundant eosinophilic granular cytoplasm sometimes in a cribriform or solid growth pattern.

6.4. Role of intraoperative frozen section evaluation in the surgical management of IPMNs

IPMNs can be ill-defined owing to the spread to branch ducts and smaller ductules. Therefore, the assessment of adequate margins may have to rely upon frozen section analysis [83,86,158,159]. However, frozen sections are a suboptimal method for analyzing tissue morphology, and should be used cautiously. If clear high-grade dysplasia or invasive carcinoma is present at the margin, further resection is warranted. Similarly, if exuberant papillary nodules are present at the margin, there may be abundant residual tumor in the pancreas [164]. All patients should be informed preoperatively that the resection may possibly be extended to total pancreatectomy. In contrast, the presence of lesser grades of dysplasia (moderate or low-grade) may not require any further therapy [141].

The common incidental occurrence of pancreatic intraepithelial neoplasia (PanIN)-1 and -2 in the general population may show up in frozen sections of the margin. Since low-grade PanINs can be indistinguishable from low-grade IPMNs [160], it may be preferable to report that "no in situ or invasive carcinoma is identified; intraductal/intraepithelial neoplasm of low/moderate grade, either PanIN or low-grade IPMN, is present". In addition, a section of the margin may show nothing but inflammation and denuded epithelium. The pathologist cannot render a diagnosis without an intact epithelium, and this should be reported as "denuded epithelium and inflammation", with such cases being carefully analyzed clinically because the denudation may prove to be the presence of an adjacent tumor [161].

6.5. Special instructions for specimen processing to differentiate BD-IPMN from MD-IPMN

Dilation of the MPD and neoplasia of the duct lining are not always correlated. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN according to the distribution of the neoplasm. There are no special instructions for specimen processing to differentiate BD-IPMN from MD-IPMN. The most important points are to identify the MPD as precisely as possible when processing the specimen, to sample the cystic lesion completely, and to examine the resected specimen thoroughly. There are different approaches to the dissection of these specimens [27,162].

6.6. Distinction of carcinoma derived from and concomitant with an IPMN

PDAC may develop independently in the pancreatic duct separately from an IPMN [39,163,164]. When PDAC originates in the vicinity of an IPMN, the distinction between PDAC derived from the IPMN and PDAC concomitant with the IPMN is sometimes difficult. Definitions of these conditions were proposed by the Japan Pancreas Society, mainly with regard to the topological relationship and histological transition between IPMN and PDAC [163]. Among 765 patients with resected IPMN, there were 183 patients with invasive carcinoma (24%). Of these, 122 (66%) were classified as PDAC derived from IPMN, 31 (17%) as PDAC concomitant with IPMN because the two lesions were discontinuous, and 30 (16%) as undetermined. It is also imperative to make every effort to distinguish between a retention cyst occurring from PDAC and IPMN accompanying PDAC. Retention cysts may be lined with epithelium with regenerative atypia or even by cancer cells extending from the PDAC, whereas IPMN is characterized by dilated pancreatic ducts lined with dysplastic mucinous epithelium showing micropapillary or macropapillary projections.

7. Methods of follow-up (Fig. 2)

7.1. Follow-up of non-resected IPMN

The decision to follow an IPMN is a matter of clinical judgment based on the patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference. There is little evidence in the literature to guide the frequency and type of surveillance for IPMNs.

At baseline, history/physical examination and MRI/MRCP (or pancreatic protocol CT) surveillance, and EUS when the presence of a mural nodule is suspected, are recommended. If the expertise is available, consideration may be given for EUS with cytopathology [3,51,71–73], CEA, [46,55,165], and molecular analyses [46,165–167].

For surveillance, patients without "*high-risk stigmata*" should undergo short interval (3–6 months) pancreatic MRI/MRCP (or CT) to establish the stability, if prior imaging is not available. Subsequently, surveillance should be performed according to the size stratification (Fig. 2). There are no good long-term data to indicate whether surveillance can be safely spaced to every 2 years or even discontinued after long-term stability. Concern over the development of PDAC in the pancreas harboring IPMN has prompted some investigators to continue surveillance at short intervals [39,136–138,163,164,168–173].

If surgically fit, patients with "*high-risk stigmata*" detected on surveillance should undergo resection. Shorter interval surveillance (3–9 months) should be considered in patients whose IPMN progresses toward these indicators or patients who already have "*high-risk stigmata*" and, for reasons of operative risk or personal preference, have chosen heightened surveillance over resection. The issue of whether a rapid growth rate is correlated with an increased risk of malignancy remains unclear, but shorter interval surveillance is recommended in such patients [92].

7.2. Follow-up of surgically resected IPMN and MCN

7.2.1. Recurrence of MCN following resection

MCNs are almost always solitary and complete resection of a non-invasive MCN is curative, thus necessitating no postoperative surveillance [74,98–100,174–176]. Although patients with invasive MCN have a poorer prognosis [98,100,174–176], the interval to follow-up imaging should match that of PDAC, despite a lack of proof that surveillance imaging improves the prognosis compared with a strategy based on symptom recurrence.

7.2.2. Follow-up and recurrence of IPMN following resection

Clinically relevant residual IPMN lesions may persist in patients postoperatively because (1) a known BD-IPMN was left unresected, (2) the surgical margins were found to have residual IPMN, and/or (3) new lesions developed in the remnant pancreas. Again, some investigators continue surveillance at short intervals owing to concern over the development of PDAC in the pancreas after resection of IPMN [39,136–138,163,164,168–173].

a) *Known IPMN in the remnant pancreas*: Patients with multifocal BD-IPMNs may have known IPMN in the remaining pancreas following IPMN resection. These patients should be followed as non-resected IPMNs (Item 7-1).

b) *Postoperative follow-up based on the resection margin status*: The resection margin may show (1) normal pancreatic tissue, (2) non-dysplastic changes (PanIN-1A or -1B), (3) low-grade dysplasia, (4) moderate-grade dysplasia, (5) high-grade dysplasia, or (6) invasive carcinoma [83].

1, 2) Normal columnar or mucinous metaplasia (PanIN-1A or -1B) should be considered as negative margins [86]. Such patients should undergo follow-up as per the guidelines for unresected

IPMN, if any, in the remnant pancreas (Item 4-2). If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable to check for new recurrence (see below).

3–5) It is unclear whether a margin that is microscopically positive for moderately dysplastic IPMN increases IPMN recurrence. For patients with low-grade or moderate-grade dysplasia at the margin, there is little evidence to guide the frequency and type of surveillance required to detect IPMN recurrence. We suggest that history/physical examination and MRCP surveillance are performed twice a year in cases of non-invasive IPMN following resection, and perhaps more often if symptoms, signs, radiographic findings, or cytopathology dictate a shorter interval of surveillance [173].

c) *New postoperative IPMN recurrence*: The rate of new recurrence of non-invasive IPMN following resection is difficult to determine from the literature, because MPD dilation in the distal pancreas following resection may be secondary to anastomotic stenosis or caused by true IPMN recurrence, and better imaging in the postoperative setting may reveal a previously undetected IPMN.

Despite these limitations, the recurrence rates in the first 5 years were reported to be 0–20% [4,85,86,177–181]. If there are no residual lesions and the margins are negative, repeat examinations at 2 and 5 years may be reasonable to check for new recurrence, although this guidance is not evidence-based. Several recent reports of distinct PDAC development in patients with BD-IPMN suggest that CT or MRCP at 6-month intervals is appropriate for surveillance, in view of the 0.7–0.9% yearly risk of PDAC development [39,136–138,163,164,168–173].

7.2.3. Recurrence of invasive IPMN following resection

The prognosis of invasive IPMN is globally better than that of conventional PDAC. However, in cases of stage II/III invasive IPMN, the prognosis is similar to that of PDAC [16,182,183]. The follow-up strategy should be identical to that for PDAC.

7.3. Possible occurrence of PDAC in patients with IPMN on follow-up and impact of family history of PDAC

Very little evidence exists to guide the management of patients with an IPMN and a family history of PDAC. Therefore, recommendations regarding the care of these individuals must draw upon what is known for familial PDAC. The risk of an individual developing PDAC based on family history alone has been well established [184,185]. An individual with one first-degree relative with PDAC has a 2.3-fold increased risk. The risk increases to 6.4-fold with two affected first-degree relatives and 32-fold with three affected first-degree relatives. A risk prediction calculator called PancPRO is available free online at http://astor.som.jhmi.edu/BayesMendel/pancpro.html [186]. In some individuals, the actual genetic defect is known and forms part of a described syndrome. The best characterized genetic defects include *BRCA2*/Fanconi anemia pathway defects (relative risk, 3.5–10-fold [187,188]), familial atypical mole malignant melanoma (FAMMM) syndrome (relative risk, 9–47-fold [189–191]), and Peutz–Jeghers syndrome (relative risk, 132-fold [192]).

The initial assessment of an IPMN should include a detailed family history and an estimate of the relative risk of developing PDAC based on the above sources. Patients with one affected first-degree relative can be followed closely using the same criteria for patients without a family history. For individuals with two or more affected first-degree relatives, the risk rapidly escalates and merits more aggressive surveillance, but does not necessarily require a recommendation for resection. In this risk category, patients with a newly diagnosed BD-IPMN should undergo high-quality MRI/MRCP or CT and EUS. In addition to "*malignant stigmata*", "*worrisome features*" are of more concern. If present, resection should be considered if the patient is surgically fit. If absent, the patient should be followed by MRI/MRCP or CT at 3-month intervals and EUS annually for the first 2 years to evaluate the development of "*worrisome features*". Patients with a cyst that shows rapid growth or develops "*worrisome features*" should be strongly considered for resection.

7.4. Possible occurrence of malignant neoplasms in other organs in patients with IPMN on follow-up

Synchronous and metachronous occurrence of malignant diseases in extrapancreatic organs in patients with IPMNs has an incidence of 20–30% [193]. Most reports describe the occurrence of malignant conditions as a part of the patient's past history [194]. However, extrapancreatic malignancies can occur even after resection of an IPMN. Therefore, attention should be paid to this phenomenon even after resection of an IPMN.

The frequency and location of extrapancreatic malignancies differ from country to country. Gastrointestinal cancer is common in Asia [195,196], while skin, breast, and prostatic cancers are frequent in the United States [197,198]. These facts may indicate that extrapancreatic malignancies occur depending on the incidences of cancer in the general populations in different regions [194].

The relationships between the types of IPMN and extrapancreatic malignancies are controversial. Some authors reported that extrapancreatic malignancies occur in all types of IPMN [194], while others reported that transcription of MUC2 may be related to the synchronous extrapancreatic gastrointestinal cancer development seen with IPMN [199].

At present, there are no screening recommendations for detecting extrapancreatic malignancies, but once the diagnosis is made, consideration of extrapancreatic neoplasms should be undertaken based on the frequency of malignancies in the general population of the country or region. Two reports have recommended screening of colorectal polyps and cancer in the United States [198,200].

8. Conclusions

Our understanding of IPMNs of the pancreas continues to evolve. Although many new publications are available since the first guidelines were published 6 years ago, the vast majority of the data are retrospective and uncontrolled, and long-term follow-up has been limited, meaning that our knowledge of the natural history of this disease is still incomplete. In this revision, the criterion for characterizing MD-IPMN has been lowered to MPD dilation of >5 mm, without losing specificity for radiologic diagnosis. "*High-risk stigmata*" and "*worrisome features*" have been defined to stratify the risk of malignancy in BD-IPMN and consider resection or increased frequency of surveillance. Resection is still recommended in all surgically fit patients with MD-IPMN or MCN. The indications for resection of BD-IPMN are more conservative. BD-IPMNs of >3 cm without "*high-risk stigmata*" can be observed without immediate resection. Methods and intervals of surveillance are proposed with an algorithm in view of "*high-risk stigmata*" and "*worrisome features*". The issue of whether the interval of surveillance can be lengthened after 2 years of no change is controversial. Some authors advocate continuation of surveillance every 6 months in view of the relatively high incidence of PDAC in patients with BD-IPMN. For MCNs of <4 cm without mural nodules, laparoscopic as well as limited resections should be considered. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs, while limited resections without lymphadenectomy or splenectomy are

reserved for those without suspicion of malignancy. The histologic types of invasive carcinoma, colloid versus tubular, and subtypes of IPMNs have prognostic implications. During resection, frozen section analysis of the surgical margin is required to ensure there is no high-grade dysplasia or invasive cancer. IPMNs need post-operative surveillance based on the resection margin status. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice yearly.

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