Review Article

International consensus on the management of intraductal papillary mucinous neoplasm of the pancreas

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Abstract: International consensus guidelines for the management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas revised in 2012 (Fukuoka consensus) seem to be accepted well worldwide. Division of various factors to predict malignant transformation into two categories, i.e., "high-risk stigmata" and "worrisome features", is also accepted as practically useful for stratifying the risk factors. Our current interest resides in the development of noninvasive and/or invasive pancreatic cancer in areas of the pancreas distinct from IPMN. Invasive pancreatic cancers derived from and concomitant with IPMN should be distinguished to clarify the incidence of each entity, although some more definitive method for differentiation has to be devised in some cases where histological distinction is obscure. IPMN is a clue to early detection of pancreatic cancer. The optimal surveillance protocol for IPMN on observation should be determined in consideration of both of these different pancreatic cancers.

Keywords: Intraductal papillary mucinous neoplasm (IPMN); main duct type; branch duct type; pancreatic cancer

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a fascinating entity caused by proliferation of mucin-producing neoplastic epithelia and characterized by cystic or saccular dilation of the branch duct (BD-IPMN) and/or main duct (MD-IPMN) (1). IPMN with macroscopic features of both BD-IPMN and MD-IPMN is called mixed type at present (*Figure 1A-C*). An orifice of the duodenal papilla may be dilated with protruding mucin and present with "fish mouth appearance" in any type of IPMN but not in all cases (*Figure 2*). This unique endoscopic feature originally drew attention in Japan and led to the emergence of a new clinical entity "mucin-producing tumors of the pancreas" (2,3).

The clinical definition and management of IPMN were rather confused for a long time until the international consensus guidelines were issued by the International Association of Pancreatology in 2006 and revised in 2012 (1,4). These guidelines were widely used for consideration of surgical resection and observation. This review addresses the most important aspects of IPMN, i.e., association of pancreatic cancer and the consensus on the management of IPMN.

Malignant change in IPMN

IPMN is characterized by malignant transformation from low-grade dysplasia to high-grade dysplasia (HGD) and further to invasive carcinoma following adenoma-carcinoma sequence (5). MD-IPMN is more frequently associated with this malignant transformation than is BD-IPMN (4), necessitating surgical resection in more than a half of the patients, while most patients with BD-IPMN can be observed for a long time after the diagnosis. Overall, the prognosis after resection is generally favorable as long as its invasion remains within minimally invasive or in T1a status (the depth of stromal invasion <5 mm) (6).

As the definitive diagnosis of the malignant change is practically difficult, the presence of malignancy has to be predicted by combination of physical and imaging findings. Accumulation of evidences yielded the Sendai consensus for prediction of malignancy and the clinical management

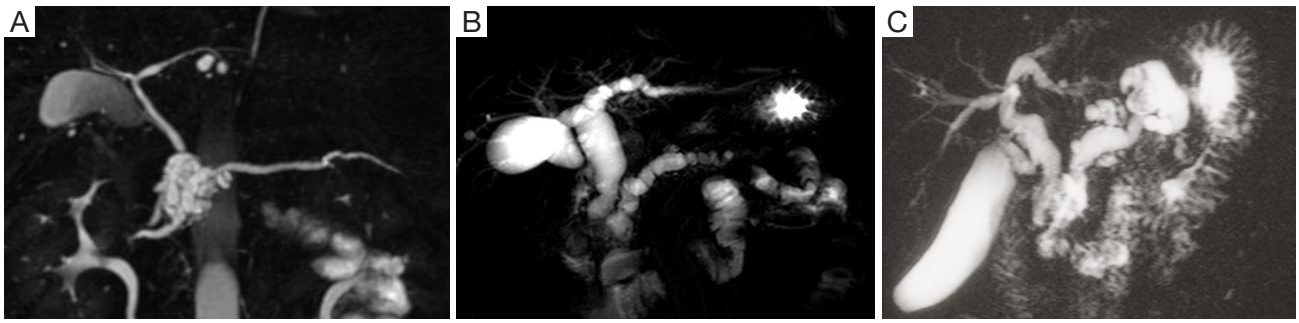

Figure 1 Magnetic resonance cholangiopancreatograms showing macroscopic types of IPMN. (A) Branch duct type; (B) main duct type; (C) mixed type.

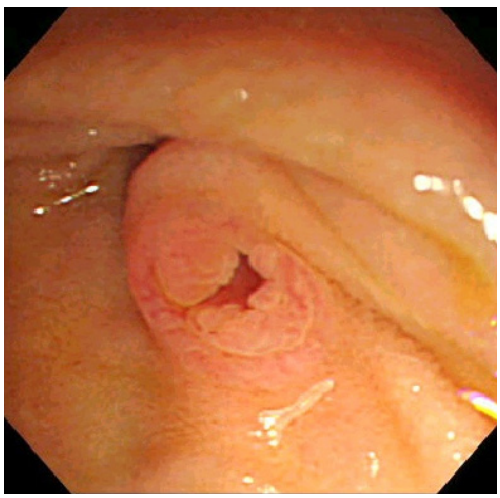

Figure 2 Endoscopic photograph of the patulous duodenal papilla dilated by mucin.

of IPMN in 2006 (4). MD-IPMN with dilation of the main pancreatic duct (MPD) >10 mm is frequently malignant and thus definitely a surgical indication. Regarding BD-IPMN, the criteria for resection consisting of clinical symptoms, positive cytology, presence of mural nodules, dilation of the MPD >6 mm, and cyst size >3 cm were accepted well and called the "Sendai criteria". Of them, the presence of mural nodules most accurately demonstrated by endoscopic ultrasonography (EUS) is most reliable to predict malignancy (7-9). Ohno *et al*. (10) further categorized mural nodules into 4 types, i.e., low papillary, polypoid, papillary, and invasive. Of these, the papillary type and invasive type were claimed as most likely indicative of malignancy. On the other hand, the size of the mural nodule to predict malignancy has been various, being 5 mm (11,12), 7 mm (13), or 10 mm (14). The size of mural nodules to predict malignancy needs to be evaluated further.

Although the cyst size >3 cm was not claimed as an absolute indication for resection in the Sendai guidelines, many patients have been recommended surgery employing this criterion with relatively low rates of malignancy in surgical specimens, only 13-23% (15,16). On the contrary, there have been a few reports of invasive carcinoma found in BD-IPMNs ≤3 cm without mural nodules (17,18), although whether HGD should be included in malignancy or not remains undetermined. The relationship of the risk of malignancy to the cyst size should be evaluated independently of the effect of mural nodules or MPD dilation. Sadakari *et al*. (15) reported the frequency of malignancy of only 3.6% in BD-IPMNs ≥30 mm without mural nodules or MPD dilation (<5 mm), whereas it was 26.3% when the MPD diameter was ≥5 mm or more. Fritz *et al*. (19) reported that 17 of 69 patients (24.6%) with BD-IPMNs <3 cm showed malignant histological features (invasive carcinoma or carcinoma *in situ*), but EUS was not performed in all of their patients. In this regard, Wong *et al*. (17) confirmed the absence of Sendai criteria by EUS in 105 patients with BD-IPMN surgically resected. Twenty-four (34%) of 70 cysts ≤3 cm patients had invasive cancer, including 1 of 7 cysts (14%) <1 cm, 2 of 19 cysts (11%) 1-2 cm, and 21of 44 cysts (48%) 2-3 cm, while 15 of 35 cysts (43%) >3 cm had invasive cancer. Sixteen cysts <3 cm (23%) had HGD, including 3 of 7 cysts (43%) <1 cm, 3 of 19 cysts (16%) 1-2 cm, and 10 of 44 cysts (23%) 2-3 cm. Likewise, Shimizu *et al*. (13) analyzed 160 patients with malignant IPMN (noninvasive 100, invasive 60) who underwent EUS and claimed that 9.4% of them had no mural nodules. Koshita *et al*. (20) also reported that 9 of 21 patients with invasive cancer derived from IPMN had no mural nodules even on EUS. Therefore, the guidelines needed to be revised in 2012 (Fukuoka consensus), where the size criterion has been excluded from high-risk stigmata

Table 1 Predictors of malignancy in branch duct IPMN

Category	Sendai consensus	Fukuoka consensus
High-risk stigmata	Presence of mural nodules; MPD >6 mm; symptoms; positive cytology (cyst size >3 cm)[§]	Enhanced mural nodules; MPD ≥10 mm; jaundice associated with a cystic mass in pancreatic head
Worrisome features		Cyst size ≥3 cm; thickened enhanced cyst walls; MPD 6-9 mm; non-enhanced mural nodules; MPD stenosis with distal pancreatic atrophy; adjacent lymphadenopathy

[§], cyst size >3 cm is not an absolute indicator of malignancy until more evidences are available. IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.

and moved down to the next category worrisome features to require thorough EUS examination (*Table 1*) (1). Goh *et al*. (21) reported that the high-risk stigmata of the Fukuoka consensus guidelines provided higher positive and negative values to predict high-risk IPMN than the Sendai consensus, 88% *vs*. 67% and 92.5% *vs*. 88%, respectively.

Some other strategies may be more effective to predict malignancy in IPMN but more complicated. Kang *et al*. (22) reported that a greater rate (4.1 mm/year for malignant *vs*. 1.0 mm/year for benign; P=0.001) of cyst growth may be of additive value to predict malignant IPMN. Shimizu *et al*. (23) proposed a nomogram comprising multiple factors to raise the sensitivity of predicting malignancy. Ohtsuka *et al*. (24) indicated that an increase in the number of predictive factors in the Sendai consensus raised likelihood of malignancy.

Cytology of the pancreatic juice collected during ERCP or cyst fluid obtained by EUS-guided fine needle aspiration (FNA) is definitely the most reliable predictor of malignancy in IPMN. However, there are disadvantages inherent to ERCP and EUS-FNA, including complications associated with these endoscopic procedures (25,26), difficulty in cytological interpretation of obtained samples, and relatively low sensitivity even with enthusiastic potential improvements (27-33). Duodenal fluid may be a right choice to explore more safe and effective prediction of malignant IPMNs provided more sensitive biomarkers are identified in the future (34-37).

Pancreatic cancer distinct from IPMN

Another unique feature of IPMN recognized 17 years after the first recognition of this fascinating entity is the association of pancreatic ductal adenocarcinoma (PDAC) concomitant with but distinct from IPMN (38,39). Since Tanaka *et al*. (38) reported the first case of carcinoma in situ concomitant with a small benign BD-IPMN in 1997, synchronous and/or metachronous association of noninvasive and invasive ordinary pancreatic cancer continues to be reported mainly in Japan (40-45). As IPMN is very easy to detect by various imaging modalities such as ultrasonography, computed tomography, and magnetic resonance imaging, IPMN has become a definite target for early detection of sporadic pancreatic cancer (46,47). Although the frequency of concomitant pancreatic cancer in patients with IPMN is not very high, being 2.5% to 9.2% (48,49), the prevalence of IPMN is relatively high as reported to be 9.4% in 341 patients undergoing EUS for non-pancreatic indications (50). This means that the increased awareness of this phenomenon should lead to early detection of pancreatic cancer.

The incidence of distinct pancreatic cancer in patients with IPMN was evaluated in many retrospective studies (40,41,43,45,51-56). Tada *et al*. (40) discovered 5 PDACs (2.5%, 0.68% per year) in 197 patients with cystic pancreatic lesions, including 80 IPMNs and 117 "non-IPMN cysts" during an average of 3.8 years. Uehara *et al*. (41) conducted a prospective study on 60 patients with BD-IPMN <10 mm on US for a mean period of 87 months. PDAC developed in a part distinct from IPMN in 5 of them (8%), thus the 5-year rate 6.9% and yearly incidence 1.1%. On the contrary, malignant transformation was noted only in 2 of 60 patients with IPMNs (3%). Tanno *et al*. (51) found 4 patients with PDAC (7.2 per 1,000 patient-years) in 89 patients with BD-IPMN followed up for a median of 64 months (range, 25-158 months). The same group found synchronous or metachronous PDAC in 9 of 168 patients (5.4%) with BD-IPMN (43). There was statistically significant tendency toward the occurrence of PDAC in patients with the older age ≥70 years, female gender, smaller cyst size and MPD diameter.

A large-scale retrospective collective study by the

Japan Pancreas Society showed distinct PDAC in 7 of 349 patients (2.0%) with BD-IPMN during a median follow-up period of 3.7 years, thus the yearly incidence 0.41% (45). On the other hand, 62 patients (17.8%) displayed progression of index IPMN. Most recently, Lafemina *et al*. (57) also reported a retrospective analysis of 170 patients with BD-IPMN with a median follow-up of 40 months. Of 97 patients who underwent resection, 79 had noninvasive IPMN and 18 "invasive carcinoma". Of note is the fact that 5 of the 18 patients with invasive carcinoma developed PDAC in a region distinct from monitored IPMN (5.2%).

The diagnosis of concomitant PDAC is quite a new problem in the management of IPMN. PDAC may be overlooked even in cross-sectional images regularly obtained at 6-month intervals (58). Ingkakul *et al*. (42) reported elevated serum CA19-9 levels and worsening diabetes as significant predictors of 22 concomitant PDACs (9.3%) in 236 patients with BD-IPMN. Kanno *et al*. (59) also reported abnormal serum CA19-9 levels as a predictor of 7 PDACs concomitant with BD-IPMN in 159 patients.

Contrast enhanced CT, MRI, and EUS are usually employed for detection of PDAC concomitant with IPMN. Sakamoto *et al*. (60) reported a patient with a 10-mm PDAC found by EUS in the pancreatic tail distinct from a BD-IPMN in the pancreatic body. The PDAC was vaguely visualized by EUS and clearly delineated by contrast-enhanced harmonic EUS. The same group eventually reported 17 invasive IPMN and 11 concomitant PDACs in 167 patients with BD-IPMN (61). Noteworthy is that they further surveyed 102 patients whose BD-IPMNs had no high-risk stigmata or worrisome features by semiannual EUS and annual US, CT, and MRI. They found distinct PDAC in 7 patients, while no single patient showed invasive progression of monitored IPMN during surveillance for a median of 42 months, thus the 3- and 5-year rates of concomitant PDAC 4.0% and 8.8%, respectively. Only 3 of the 7 PDACs (43%) were visualized by CT or MRI even after detection by EUS. US could not detect any of the 7 PDACs. EUS seems to be essential for early detection of PDAC concomitant with IPMN. Ohtsuka *et al*. (56) further emphasized the significance of ERCP cytology for very early detection of PDAC in patients with IPMN.

The precise incidence of distinct PDAC arising in patients with IPMN and roles of diagnostic modalities in the early detection are to be determined by a large-scale prospective surveillance currently under way by the Japan Pancreas Society.

Fukuoka consensus

The two major changes in clinical management of IPMN reached in the Fukuoka consensus are a lowered threshold (≥5 mm) of the size of the MPD to increase the sensitivity of the diagnosis of MD-IPMN, and the introduction of two-layer criteria to predict malignancy in IPMN, i.e., "high-risk stigmata" to recommend immediate resection in all fit patients and "worrisome features" to warrant thorough examinations by EUS (*Figure 3*) (1). This revision is now widely accepted with higher sensitivity of the diagnosis of IPMN and prediction of malignancy (9,21), although the adequacy of the cyst size moved from the "high-risk stigmata" to "worrisome features" is still giving rise to much controversy (8,9,17,19). One meta-analysis declaimed that the cyst size >3 cm was associated most strongly with malignant IPMN (8), whereas another meta-analysis published later insisted that the presence of mural nodules should be regarded most highly suspicious of malignancy (9).

The Fukuoka consensus on pathological analyses of resected specimens of IPMN is that noninvasive carcinoma should be called HGD. As mentioned before, whether HGD should be operated on or can be observed remains unknown, because the natural history of IPMN progression after malignant transformation or the length of the period for HGD to become invasive carcinoma is not known. Although our previous study demonstrated that both HGD and T1a carcinoma (depth of invasion <5 mm) of IPMN (formerly called minimal invasion) are associated with a 100% survival rate after resection, it would be generally justifiable for most investigators to want to include HGD into the surgical indication, because the T1a carcinomas may already accompany lymph node metastasis in 20% (6).

Our particular interest resides in the appropriate methodology and time intervals for surveillance of BD-IPMN to check the malignant changes and development of distinct PDAC. The Fukuoka consensus advocates yearly follow-up if lesion is <10 mm in size, 6-12 monthly follow-up for lesions between 10 and 20 mm, and 3-6 monthly follow-up for lesions >20 mm as current reasonable approaches to surveillance, although the appropriate intervals between follow-up examinations remain to be determined. The Fukuoka consensus also recommends lengthening of the surveillance interval after 2 years of no change on images as did the Sendai guidelines. On the other hand, however, the Fukuoka consensus proposes not to lengthen the intervals to >6 months in view of the relatively high incidence of concomitant PDAC. This is an obvious

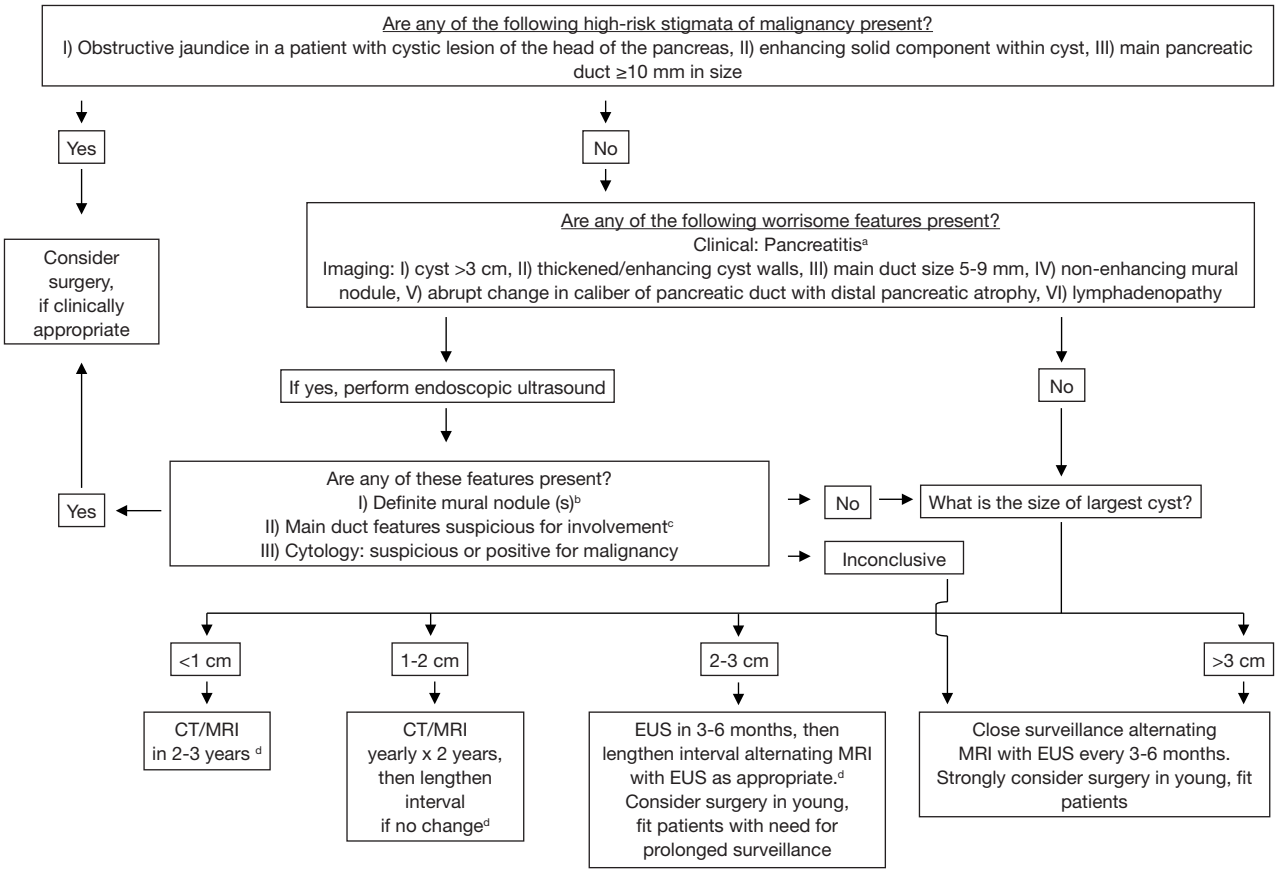

Figure 3 Management algorithm with two-layer criteria to stratify risk factors to predict malignancy. Cited and reproduced with permission from Pancreatology 2012;12:183-197. [a], pancreatitis may be an indication for surgery for relief of symptoms. [b], differential diagnosis includes mucin. Mucin can 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 inconclusive. [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.

flaw of the Fukuoka consensus and large-scale prospective studies are awaited to solve a contradiction between those two statements. A French group reported a low incidence of malignant transformation and adequacy of lengthening of the follow-up intervals, but they still recommended biannual imaging studies (62). Tamura *et al*. (58) claimed that even a 6-month interval might not be sufficient to diagnose a concomitant PDAC in a patient with IPMN.

The length of surveillance for IPMN is another concern for every clinician. Although the Fukuoka consensus states that 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, the guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts issued by the American Gastroenterology Association (AGA) in 2015 recommends stopping the surveillance of pancreatic cysts in 5 years of no significant changes, if high-risk features are completely negated and the patient does not have a strong family history of PDAC. They state that the small risk of malignant progression in stable cysts is likely outweighed by the costs of surveillance (63). However, there have not ever been any evidences reported on continuance or discontinuance of surveillance of IPMN.

It appears that the pancreas may be affected by "field carcinogenesis" in patients with IPMN. IPMN is quite often multiple as reported as up to 83% (64). Multiple IPMNs, ≥10 in number, were reported to be associated with higher prevalence of HGD or invasive carcinoma including concomitant PDAC (65). Moreover, even multifocal PDACs may be present in patients with IPMN (66). The "field carcinogenesis" may also give rise to PDAC even after resection of invasive or noninvasive IPMN or concomitant PDAC, requiring life-long close surveillance (52,55,64). In this regard, the AGA guideline will need to be revised in the near future. As the "field carcinogenesis" of the pancreas may have some relationship with multiple IPMNs and concomitant pancreatic intraepithelial neoplasia (PanIN) or PDAC in patients with familial PDAC (67), a family history of PDAC should be carefully taken as the AGA guideline states as well.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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