Controversies in the management of pancreatic IPMN

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Strapline: Opinion

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Abstract

Although considerable progress has been made in our understanding of intraductal papillary mucinous neoplasm (IPMN) of the pancreas, some questions still remain to be answered, which are discussed in this Perspective. First, the uncertainty regarding the classification of IPMNs needs to be eliminated. Second, the necessity of the mixed-type category and whether it should be defined radiographically or histologically needs to be determined. Since premalignant mucinous cysts (such as IPMNs and mucinous cystic neoplasms) are surgical indications, the preoperative distinction of branch duct IPMNs from nonmucinous cysts should also be investigated. The role of cystic fluid analysis remains to be clarified in this context as well as its safety. With regard to the diagnosis of malignancy in branch duct IPMNs, the presence of mural nodules is a very reliable predictor. However, controversy exists over the value of size as a reliable indicator of malignancy. Criteria with increased specificity are required, perhaps including histological subtypes of lesion, to reduce this false positive rate of the present criteria for malignancy. Branch duct IPMN surveillance is threefold: malignant transformation, development of distinct ductal adenocarcinoma and disease recurrence after resection. The best modality and interval for surveillance remain unknown, although the interval should not be longer than 6 months.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a relatively new entity that is being diagnosed with increasing frequency. The first case in the world was reported in 1980 in a patient with marked dilatation of the main pancreatic duct, profuse production of mucin and a pancreatobiliary fistula.[1] Approximately a decade later, IPMN became established as a clinical entity distinct from mucinous cystic neoplasm (MCN).[2] Since the publication of international consensus guidelines for the management of IPMN and MCN in 2006 after the Sendai meeting of the International Association of Pancreatology, IPMN of the pancreas has been drawing increasing attention.[3] Although the guidelines contributed to increased awareness and better understanding of IPMNs and improved management of patients with this entity, many issues still remain to be resolved (Box 1). This Perspective aims to discuss several aspects of this fascinating disease that deserve further attention, including the classification of mixed-type IPMNs, differential diagnosis of these lesions from other cystic neoplasms, criteria for the resection of branch duct IPMNs and surveillance, which have arisen after widespread use of the consensus guidelines.

Classification

At present, IPMNs are classified into three types: branch duct, main duct and mixed or combined.[4] This classification is based on the dominant location of the IPMN where the ductal dilatation occurs. The vast majority of patients have either branch duct or main duct IPMNs. However, a small proportion of patients have mixed-type IPMNs, in which the ductal dilatation involves one or a few branch ducts and a large part of the main duct. Classification of IPMNs is based either on radiographic morphology or histology with preference for either differing between institutions. As histological examination of branch duct IPMNs often reveals involvement of the main duct, the proportion of patients with mixed-type IPMNs becomes very high if the classification is only based on histological findings. Indeed, some pathologists may be reluctant to classify IPMNs as one type or another knowing that most IPMNs when evaluated histologically fall into the mixed-type category. However, the preoperative classification of IPMNs is important because it affects therapeutic

decision-making. The classification of IPMNs and the value of the mixed-type category need to be determined more clearly.

Analysis of the histological and clinical characteristics of a large number of IPMNs (comprising 159 branch duct, 81 main duct and 149 mixed) showed that the frequency of invasive carcinoma in branch duct, main duct and mixed IPMNs was 11%, 48% and 42% , respectively.[5] Therefore, mixed IPMNs seem to have similar clinicopathological features to main duct IPMNs. To eliminate uncertainty in the classification of IPMNs, the issue of whether the mixed type should be defined radiographically or histologically needs to be resolved.

Distinction of branch duct IPMNs

Branch duct IPMNs should be distinguished from a variety of cystic neoplasms of the pancreas, including MCNs, macrocystic or oligocystic serous cystic neoplasms, epidermoid cysts, lymphoepithelial cysts, chronic or acute pseudocysts and cystic varieties of some other neoplasms. Careful history taking, laboratory tests and imaging findings are helpful when considering a differential diagnosis. However, even on the basis of a thorough understanding of the characteristics of each entity,[3] IPMNs, MCNs and macrocystic or oligocystic serous cystic neoplasms are sometimes difficult to differentiate preoperatively.

Cystic fluid analysis

The ability to distinguish mucinous cysts like IPMNs and MCNs with malignant potential from nonmucinous cysts is particularly important. In this regard, the role of analyzing cyst fluid obtained by endoscopic ultrasonography (EUS)-guided fine-needle aspiration has been enthusiastically investigated (Table 1).

Several studies that have investigated the validity of biomarkers to distinguish lesions have reported that a high level of carcinoembryonic antigen (CEA) (>367[6], >800[7], ≥480[8] and >800 [9] ng/ml) can be used to discriminate between mucinous and nonmucinous cysts. In a study of 112 patients with pancreatic cysts, the accuracy of a CEA level >192 ng/ml in cystic fluid for the diagnosis of a mucinous cyst was 79%, and significantly better than the accuracy of either EUS imaging (51%), cytology (59%) or these two procedures combined (P<0.05).[10] However, poor agreement

between CEA levels and molecular analysis for the diagnosis of mucinous cysts has been reported, although the diagnostic sensitivity of such tests improved when the results were combined.[11] In addition, one study has reported that the CEA level in cystic fluid was higher (median 471 ng/ml) in 50 potentially malignant or malignant MCNs and IPMNs than in 29 benign cysts (median 1 ng/ml).[12]

Haab *et al.*[13] demonstrated that detection of a glycan variant of MUC-5AC discriminated IPMNs and MCNs from nonmucinous benign cysts with a sensitivity of 78% and a specificity of 80%. Furthermore, sensitivity and specificity improved to 87% and 86%, respectively, when this molecular test was combined with measurement of cystic fluid level of CA (carbohydrate antigen) 19-9. By contrast, measurement of CEA level on its own had a low sensitivity (37%) and specificity (80%) in this study. Although mucin-like carcinoma-associated antigen levels, *KRAS* mutations and CA72-4 levels are claimed to be helpful in the diagnosis of mucinous cysts, the role of cystic fluid analysis and its biomarkers in preoperative differentiation between mucinous and nonmucinous pancreatic cysts requires further evaluation.[14–16]

Adequacy of the Sendai criteria

The international guidelines for the management of IPMN and MCN advocate resection of all main duct IPMNs and some branch duct IPMNs that meet one or more of five criteria for suspected malignancy: pancreatic juice cytology positive for malignancy, the presence of mural nodules, cyst size >3 cm, dilatation of the main pancreatic duct, and abdominal pain (Figure 1).[3] Besides positive pancreatic juice cytology, the presence of mural nodules is the most reliable predictor of malignant changes in branch duct IPMNs.[17–20] However, the size criterion is a matter of controversy and remains unresolved. Although Nagai *et al.*[21] reported that 4 of 49 patients with branch duct IPMNs or mixed-type IPMNs <3 cm without mural nodules had malignancy, several other studies have found no carcinomas among patients with purely branch duct IPMNs of <3 cm without mural nodules (Table 2).[17,22–24] In a large cohort of 145 patients with surgically resected branch duct IPMNs, malignancy was absent in patients with tumors <3 cm without mural nodules.[24] The Sendai criteria, therefore, seem to be adequate for identifying all malignancies, although only 22% (11%

carcinoma *in situ*; 11% invasive) of resected tumors in the series were malignant.[24] Likewise, a study by Tang *et al.*[25] reported that 18 of 23 (78%) branch duct IPMNs recommended for surgical resection on the basis of the Sendai criteria were benign. Salvia *et al.*[26] employed different criteria: the presence of clinical symptoms, cyst size >3.5 cm, the presence of nodules, thick tumor walls, a serum CA19-9 level of >25 U/l, and recent onset or worsened diabetes. These authors still found that 17 of 20 (85%) branch duct IPMNs selected for surgery were benign. More specific criteria certainly need to be developed to exclude such false-positive results that result in unnecessary surgical intervention.

Since the introduction of histological subclassification of IPMNs into gastric, intestinal, pancreatobiliary and oncocytic type and the recognition of differences in mucin expression between these subtypes,[27,28] the possibility of adding such subclassification to criteria for resection of branch duct IPMNs has been anticipated. Two studies found that most branch duct IPMNs were of the gastric type, whereas main duct IPMNs were usually of the intestinal type. The prognosis of branch duct IPMNs is well known to be better than that of main duct IPMNs, and hence the histological subtypes correlate with the prognosis.[29,30] Furthermore, invasive intraductal papillary mucinous carcinomas derived from nonintestinal types of IPMNs (n = 16), that is gastric type (n = 6), pancreatobiliary type (n = 8), oncocytic type (n = 1) and nonclassifiable (n = 1), showed a poorer prognosis than those derived from intestinal-type IPMNs (n = 14).[31] The preoperative determination of histological subtypes by either immunohistochemical staining[32] or molecular marker analysis[33] of the pancreatic juice or aspirated cyst fluid samples would be of paramount interest and benefit.

Surveillance of branch duct IPMNs

The optimal modality for follow-up surveillance of branch duct IPMNs without malignant signs remains to be determined. Some investigators use EUS to observe changes in the size of the cyst and main pancreatic duct,[34] and others use ultrasonography, CT and/or MRI. EUS is more sensitive than the other techniques for identifying such changes but has inherent drawbacks of invasiveness, cost as well as intraobserver and interobserver variability. The sensitivities of ultrasonography, CT and MRI should be

thoroughly examined with regard to the rate of detection of malignant changes.

The clinical significance of branch duct IPMN surveillance is threefold. First, these IPMNs are well known to exhibit malignant changes following the adenoma-carcinoma sequence;[35,36] the criteria for such malignant transformation were proposed in the 2006 guidelines and are described earlier.[3] Second, clinicians should be on guard against the development of pancreatic ductal adenocarcinoma (PDAC) at a different site in the pancreas from the IPMN. Third, even among patients who undergo partial pancreatectomy for noninvasive IPMNs, 10% are reported to experience disease recurrence.[37]

Since the occurrence of *in situ* or invasive PDAC concomitant with a benign branch duct IPMN was reported, this phenomenon has been drawing increasing attention.[38–40] Evidence indicates relatively high incidences of PDACs in patients with branch duct IPMNs (Table 3).[40-45] A study reports that PDACs were found in 5 of 60 (8%) patients with branch duct IPMNs, the initial sizes of which were <1 cm, during a median follow-up of 87 months.[41] Thus the 5-year rate of PDAC development was 6.9% and the incidence was 1.1% per year. On the other hand, malignant changes of IPMNs were noted in just 2 of 60 (3%) patients.[41] Ingkakul and co-workers[42] detected concomitant synchronous or metachronous PDACs in 22 of 236 (9.3%) patients with IPMNs. All 22 IPMNs were branch duct IPMNs and histology indicated that 12 resected IPMNs were benign. Worsening diabetes and high levels of serum CA19-9 predicted the presence of PDAC on the basis of multivariate analyses. Elevated serum levels of CA 19-9 were also a predictor of PDACs in a study by Kanno *et al.*[43] in which PDACs were noticed in 7 of 159 (4%) patients with branch duct IPMNs. Tanno and colleagues[44] found 9 of 168 (5.4%) patients with branch duct IPMNs also had PDACs. The patients who developed PDACs in this study were older and had smaller IPMN cysts and main pancreatic ducts compared with the patients who did not develop PDACs.

The main pancreatic duct should always be examined by cytology as well as frozen-section histology when a branch duct IPMN, with or even without main pancreatic duct dilatation, is resected just as in patients with main duct IPMNs.[46] The significance is twofold: to survey the presence of carcinoma concomitant with IPMN, but not detected during preoperative

work-up; and to confirm the absence of malignant transformation of IPMN undetectable by preoperative imaging examinations.

The intervals for follow-up examinations of potentially benign branch duct IPMNs and the residual pancreas after resection of IPMNs must be reconsidered in this context. The 2006 guidelines suggest that branch duct IPMNs <1 cm, 1–2 cm, and 2–3 cm in size should be examined by CT or MRI every year, every 6–12 months and every 3–6 months, respectively (Figure 1).[3] The guidelines also state that the interval of follow-up examination can be lengthened after 2 years of no change. However, this statement may need to be reconsidered in view of the relatively high incidence of PDACs that develop distinct from IPMNs in comparison with the incidence of malignant changes to the IPMN itself.

As stated above, all patients with branch duct IPMN should undergo meticulous surveillance examinations because of the alleged high risk of PDAC development, although the best interval and modality for surveillance remain to be determined. Whether patients with IPMN and a family history of PDAC have a higher risk of PDAC than patients with IPMN but without a family history of PDAC remains to be determined. Furthermore, patients with a strong family history of PDAC are likely to develop IPMNs and subsequently a PDAC during follow-up.[47,48] Whether those patients with IPMN and a family history of PDAC need more frequent surveillance is also unknown.

Conclusions

Clarification of the classification of pancreatic IPMNs, whether the mixed type IPMN should be defined radiographically or histologically and whether this category is necessary are issues that need to be resolved. Preoperative distinction of premalignant mucinous cysts from nonmucinous cysts should be further pursued and the role and safety of cystic -fluid analysis remain to be evaluated in this context. With regard to the diagnosis of malignancy in branch duct IPMNs, criteria with greater specificity are required to reduce the false-positive rate of the 2006 international Sendai guidelines because approximately 80% of branch duct IPMNs that are resected are benign. Preoperative determination of histological subtype could be of interest and value. Surveillance of branch duct IPMNs is of the utmost importance to detect malignant transformation, the development of

distinct PDACs and disease recurrence after resection. The best modality for surveillance is not yet known, but the interval for surveillance should not be longer than 6 months.

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Figure 1| Algorithm for the management of a branch duct IPMN according to the 2006 international guidelines for the management of IPMN. MRCP: magnetic resonance cholangiopancreatography. Cited and edited from the international guidelines with permission. * The interval of follow-up examination can be lengthened after two years of no change.

Table 1. Cyst fluid analysis obtained by fine needle aspiration under endoscopic ultrasonographic guidance

Authors	Year	Cyst examined (number)	Viscosity	CEA (ng/ml)	CA19-9 (U/ml)	CA125 (U/ml)	CA72-4 (U/ml)
Lewandrowski et al. [8]	1993	MCN (n=11) high in 89%		>367		variable	
		SCN (n=5)	low	<23		variable	
		Pseudocyst (n=9) low	<23		low		
		PDAC (n=1)				high	
		Suggested level to diagnose mucinous cyst	high	>367	not reliable		
Alles AJ, et al.[16]	1994	MCA (n=4)				55.3, mean	
		MCC (n=5)				10,027, mean	
		SCN (n=5)					< 3
		Pseudocysts (n=5)				3.8, mean	
Sperti C, et al.[6]	1997	MCN (n=8)	MCAA high				
		SCN (n=6)	MCAA low				
		Pseudocyst (n=10)	MCAA low				
O'Toole D, et al.[7]	2004	MCA (n=32)		<5 in 7%	>50,000 in 78%		<40 in 73%
		Macrocystic SCN (n=9)		<5 in 100%	<50,000 in 100%		<40 in 89%
Brugge, et al. [12]	2004	MCA (n=18)		684, mean			
		MCC (n=50)*		8400, mean			
		SCN (n=7)		2.7, mean			
		Pseudocyst (n=27)		37, mean			
		Suggested level to diagnose mucinous cyst		>192			
van der Waaij, et al. [9]	2005	Pooled data of 12 studies					
		MCA	400, median (n=64)	15,000, median (n=24)			
		MCC	2,000, median (n=64)	20,000, median (n=22)			
		SCN	3, median (n=79)	500, median (n=24)			
		Pseudocyst	10, median (n=125)	4,000, median (n=66)			
		Suggested level to diagnose mucinous cyst		>800			
Linder, et al. [10]	2006	MCA (n=21)	1.84, mean	878, mean			
		MCC (n=14)	1.9, mean	27,581, mean			
		SCN (n=13)	1.27, mean	121, mean			

		Pseudocyst (n=23)	1.6, mean 189, mean
		Suggested level to diagnose mucinous cyst	=/>480
Attasaranya, et al.[11]	2007	MCN (n=14)	277, median
		NMCN (n=21)	1.5, median
		Suggested level to diagnose mucinous cyst	=/>480
Leung KK, et al.[14]	2009	Malignant/premalignant (MCA, MCC, IPMN)	471, median 14950, median (n=24) (n=9)
		Benign (SCN, pseudocyst)	1, median 1670, median (n=21) (n=7)

*MCC in this series includes 42 malignant and 8 borderline lesions.

Abbreviations. CEA: carcinoembryonic antigen; CA: carbohydrate antigen; MCN: mucinous cystic neoplasm; MCA: mucinous cystadenoma; MCC: mucinous cystadenocarcinoma; SCN: serous cystic neoplasm; PDAC: pancreatic ductal adenocarcinoma; NMCN: nonmucinous cystic neoplasm; MCAA: mucin-like carcinoma-associated antigen.

Table 2. Frequencies of malignancy in branch duct IPMNs in relation to the cyst size and mural nodules				
Study	Number of patients	Size criteria (in cm)	Mural nodules (+/-)	Malignancy (%)
Sugiyama *et al.* (1998)[21]	16	≥3	5/5	4/5 (80/100)
		<3	1/5	1/0 (100/0)
Bernard *et al.* (2002)[17]	12	≥3	0/3	0/0 (100/0)
		<3	2/7	2/0 (100/0)
Rodrigues, *et al.* (2007)[24]	145	≥3	11/36	7/13 (63.6/36.1)
		<3	12/86	12/0 (100/0)
Sadakari *et al.* (2010)[25]	73	≥3	0/47	0/6 (0/12.8)
		<3	0/26	0/0 (0/0)
Total	246	≥3	16/91	11/24 (69/26)
		<3	15/124	15/0 (100/0)
Abbreviation: IPMN, intraductal papillary mucinous neoplasm				

Table 3. **Incidences of PDACs in patients with branch duct IPMNs**				
Study	Number of patients	Number of PDACs	Follow-up	Incidence (%)
Yamaguchi *et al.* (2002)[40]	76	7	NA*	9.2
Uehara *et al.* (2008)[41]	60	5	Median 87 months	8.0
Ingkakul *et al.* (2010)[42]	236	22	NA	9.3
Kanno *et al.* (2010)[43]	159	7	NA	4.4
Tanno *et al.* (2010)[44]	168	9	NA	5.4
Ikeuchi *et al.* (2010)[45]	145	5	Mean 55.9 months	3.5
*Not applicable as study involved retrospective analysis. Abbreviations: IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma				

Box 1 Unresolved issues in the management of IPMNs
Classification of mixed-type IPMNs
Differential diagnosis of these lesions from other cystic neoplasms
Criteria for the resection of branch duct IPMNs
Extent of resection of branch duct IPMNs
Treatment of multifocal IPMNs
Lymph node involvement and dissection
Surveillance
Genetic and histopathological relationship of IPMNs to pancreatic ductal adenocarcinoma
Clinical outcome
Abbreviation: IPMN, intraductal papillary mucinous neoplasm