EDITORIAL

Which guidelines should be used for branch-duct intraductal papillary mucinous neoplasms?

Ridtitid et al[1] have highlighted the incremental value of EUS-guided FNA (EUS-FNA) over cross-sectional imaging in identifying malignant branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs), particularly in patients without worrisome features (WFs) and those with smaller cysts, in their article in this issue of *Gastrointestinal Endoscopy*. They reported that EUS-FNA features (mural nodule, main duct involvement, and malignant cytology) were highly specific and accurate for malignant BD-IPMNs. They also revealed that 28% of mural nodules seen by EUS in low-risk patients were missed by cross-sectional imaging. The impact of these results may question the recommendations of guidelines on the daily practice and clinical management of BD-IPMNs.

International consensus guidelines (ICG) (widely known as Sendai consensus guidelines) were published in 2006 for the management of IPMNs and mucinous cystic neoplasms (MCNs). BD-IPMNs under 1 cm were recommended for follow-up with magnetic resonance imaging (MRI) yearly, and cysts larger than 3 cm were recommended for resection. Cysts 1 to 3 cm in diameter were recommended for further imaging, looking for high-risk stigmata (HRS) (Table 1). Surgical resection was recommended for patients with HRS, whereas the remaining patients were triaged for surveillance based on cyst size (every 6-12 months for 1- to 2-cm cysts and 3-6 months for 2- to 3-cm cysts).[2]

ICG were updated in 2012 (widely known as Fukuoka consensus guidelines).[3] For the management of suspected BD-IPMNs, the first step of an algorithm is to look for HRS of malignancy (Table 1). When ICG is used, patients with HRS should be referred for surgical resection and others should be examined for WFs (Table 1). Patients with WFs should be directed to EUS-FNA (Table 2), and presence of any EUS-FNA features (definite mural nodule, main duct feature suspicious for involvement, or cytology suspicious/positive for malignancy) is an indication for possible resection (Table 3). In the absence of WFs, patients should be managed based on the size of the lesion. Cross-sectional imaging in 2 to 3 years was recommended for cysts < 1 cm, and annual surveillance with cross-section was recommended for cysts 1 to 2 cm. Cysts 2 to 3 cm were managed with EUS-FNA, and cysts > 3 cm were directed to surgery.[3]

In 2015, the American Gastroenterological Association (AGA) reported its guidelines on the diagnosis and management of asymptomatic neoplastic cysts.[4] MRI surveillance was recommended in patients without high-risk features (Table 1) for up to 5 years. Patients having at least 2 of these high-risk features or recent changes were directed to EUS-FNA (Table 2). Patients without concerning EUS-FNA results were referred to MRI surveillance to ensure no change in malignancy risk. The AGA guidelines were opposed to continued surveillance after 5 years in the absence of significant change in cyst characteristics. Patients with cysts with a solid component and a dilated duct and/or concerning features on EUS were recommended for surgical resection to reduce mortality risk for carcinoma[4] (Table 3).

In low risk patients, the AGA guidelines suggest surveillance with cross-sectional imaging. If there is no sign of significant change in size or morphology over 5 years, discontinuation of imaging is recommended. There is concern that these guidelines may interfere with the detection of early malignancy.

These guidelines have been validated by several large retrospective studies with conflicting results. Their clinical utility in the initial triage of pancreatic cysts based on cross-sectional imaging were evaluated with the actual surgical histology. Three hundred seventeen patients who underwent surgery were classified as "high-risk and low-risk" according to Sendai guidelines and "high-risk, worrisome and low-risk" according to Fukuoka guidelines. In the prediction of malignancy, the positive predictive value and negative predictive value of high-risk patients according to Sendai and Fukuoka guidelines were 67% and 88% and 88% and 92.5%, respectively.[5] Similarly, in a study of 177 patients who underwent surgical resection, the positive predictive values of high-risk patients according to Sendai and Fukuoka guidelines for high-grade dysplasia/invasive carcinoma were 46% and 62.5%, respectively. The negative

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TABLE 1. Selected features of BD-IPMNs used for predicting risk of malignancy by 3 consensus guidelines

	Sendai*	Fukuoka*,†	AGA‡
High-risk stigmata*	Mural nodules	Obstructive jaundice	Cyst ≥ 3 cm
High-risk features‡	Dilated MPD	Enhancing solid component	Associated solid component
	Positive cytology	MPD ≥ 10 mm	Dilated MPD
Worrisome features†		Cyst ≥ 3 cm	
		Thickened/enhancing cyst wall	
		MPD 5-9 mm	
		Nonenhancing mural nodule	
		Abrupt change in PD caliber with distal pancreatic atrophy	

MPD, Main pancreatic duct; *PD*, pancreatic duct.
*High-risk stigmata for Sendai 2006 and Fukuoka 2012.
†Worrisome features for Fukuoka 2012.
‡High-risk features for AGA 2015.

TABLE 2. Consensus guidelines for EUS-FNA in patients with BD-IPMNs

Features	Sendai 2006	Fukuoka 2012	AGA 2015
Clinical pancreatitis	N/A	+*	N/A
Cyst size	1-3 cm	≥3 cm*	≥3 cm‡
Main duct size	N/A	5-9 mm*	Dilated MPD‡
Mural nodule	N/A	Nonenhancing mural nodule*	N/A
Cyst wall	N/A	Thickened/enhancing wall*	N/A
Other	N/A	Abrupt change in PD caliber with distal pancreatic atrophy*	Presence of associated solid component‡

BD-IPMNs, Branch-duct intraductal papillary mucinous neoplasms; *N/A,* not applicable; *MPD*, main pancreatic duct; *PD*, pancreatic duct.
*Presence of any of these "worrisome features" is indication for EUS-FNA, according to Fukuoka 2012.
‡Presence of at least 2 of "high-risk features" is needed for EUS-FNA, according to AGA 2015.

TABLE 3. Consensus guidelines for surgery in patients with BD-IPMNs

Sendai (*any 1* risk factor)	Fukuoka (*any 1* risk factor)	AGA 2015 (2 risk factors and/or EUS-FNA)
Cyst size > 3 cm	Obstructive jaundice	Solid component and dilated MPD
Mural nodule	Solid component	And/or concerning features on EUS-FNA
Malignant cytology	+/suspicious cytology for adenocarcinoma	
Dilated MPD	MPD ≥ 1 cm	
Symptoms	Mural nodule on EUS	
	>3-cm cyst in young surgically fit patient	

BD-IPMNs, Branch-duct intraductal papillary mucinous neoplasms; *MPD*, main pancreatic duct.

predictive value of both according to both Sendai and Fukuoka was 100%.[6] The AGA guidelines have been validated by comparison with the EUS-FNA findings and cyst fluid analysis of 225 patients, and the guidelines identified advanced neoplasia with 62% sensitivity, 79% specificity, 57% positive predictive value, and 82% negative predictive value.[7]

Ridtitid et al[1] enrolled 364 BD-IPMN patients in their retrospective cohort study over 12 years. BD-IPMN diagnoses were based on ICG 2012 and/or pathologically confirmed pure BD-IPMNs. The association between risk factors on cross-section and malignant BD-IPMNs, performance of EUS-FNA for diagnosis of malignant BD-IPMNs, and long-term outcomes of patients were examined. In their cohort, they found a frequent association between main pancreatic duct (5-9 mm) on CT/MRI and malignant BD-IPMNs (among all HRS and WFs of the ICG 2012). EUS features, including mural nodules, main pancreatic duct features suspicious for involvement, and suspicious/malignant cytology, were accurate and highly specific for malignant BD-IPMNs, with a sensitivity, specificity, and accuracy of 33%, 94%, and 86%; 42%, 91%, and 83%; and 33%, 91%, and 82%, respectively. Mural nodules identified by EUS were missed in 28% in the malignant group, which were in low-risk cysts according to AGA guidelines. Furthermore, when applied to their cohort of patients,

TABLE 4. Consensus guidelines for surveillance in patients with BD-IPMNs

Sendai (MRI/CT based on size)	Fukuoka (MRI/CT based on size)	AGA
Nonresected IPMNs that are low-risk of malignancy (<3 cm, no solid component, no nodule, nondilated MPD, EUS-FNA not concerning)		
<1 cm: in 1 y	<1 cm: every 2-3 y	Repeat MRI in 1 y, then every 2 y
1-2 cm: every 6-12 mo	1-2 cm: every y for 2 y, then lengthen	
2-3 cm: 3-6 mo	2-3 cm: EUS in 3-6 mo, then lengthen and alternate MRI	
	>3 cm: alternate MRI with EUS every 3-6 mo	
	No explicit recommendation to stop	Stop after 5 y of stable cyst or nonsurgical patient
Cytology	**Fukuoka**	**AGA**
Resected IPMNS		
IPMN with clean margin and no residual	Consider 2 and 5 y	None
IPMN with clean margin and residual cyst	As per nonresected cysts	N/A
IPMN with any dysplasia at margin	Every 6 mo	None (except HGD, which is followed like cancer)
IPMN with cancer	Every 3 mo	2 and 4 y

MPD, Main pancreatic duct; *N/A*, not applicable; *HGD*, high-grade dysplasia; *IPMN*, intraductal papillary mucinous neoplasms.

both AGA and ICG 2012 guidelines missed 5% of patients with invasive cancer at surgery (who had cysts under 3 cm and were defined as low-risk and without WF). Patients with malignant BD-IPMNs had a higher risk of benign/malignant IPMN recurrence during follow-up.[1]

Although BD-IPMNs are detected more frequently and are classified as having a low malignancy risk compared with other mucinous cysts, the question of when EUS-FNA should be performed is controversial. In the Fukuoka guidelines, EUS is recommended in patients with a history of clinical pancreatitis and WFs, whereas the AGA guidelines recommend EUS in the presence of at least 2 high-risk features. The sensitivity and specificity of CT/MRI in detecting the presence of mural nodules is reported to be only fair to moderate.[8] Furthermore, in low risk patients, the AGA guidelines suggest surveillance with cross-sectional imaging. If there is no sign of significant change in size or morphology over 5 years, discontinuation of imaging is recommended. There is concern that these guidelines may interfere with the detection of early malignancy.

Although the Fukuoka guidelines recommend possible EUS-FNA for small BD-IPMNs without WFs in centers with expertise,[3] the AGA guidelines do not recommend EUS-FNA in small, low-risk cysts. The Fukuoka guidelines also recommend EUS-FNA in 3 to 6 months in 2- to 3-cm cysts without HRS/WFs. On the other hand, the Sendai and Fukuoka guidelines are designed to detect early neoplasia (such as high-grade dysplasia), whereas the AGA guidelines are designed for late neoplasia (invasive carcinoma). Recently, Singhi et al[7] reported that the AGA guideline missed 45% of IPMNs with high-grade dysplasia or adenocarcinoma when they applied the AGA guideline to their cohort of patients. Their pathway, based on EUS-FNA and cyst fluid analysis, had 100% sensitivity and 90% specificity.

For postsurgical surveillance, the AGA guidelines are opposed to monitoring for resected IPMNs with a positive margin (except for high-grade dysplasia). The Fukuoka guidelines suggest surveillance in 2 and 5 years when margins are clean and every 6 months when any dysplasia is present at the margin (Table 4). Because IPMNs are considered to represent a field defect[9] and several studies report adenocarcinoma recurrence up to 11%,[10] we believe more frequent surveillance should be considered after resection. If clinicians choose to follow the new AGA guidelines for their patients with BD-IPMNs, they should be aware of the risk of missing some malignant cysts in the initial evaluation and recurrent IPMNs after surgical resection.

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Omer Basar, MD
Pancreas Biliary Center, Gastrointestinal Unit
Massachusetts General Hospital
Boston, Massachusetts, USA
Department of Gastroenterology
Hacettepe Medical School
Ankara, Turkey
William R. Brugge, MD
Pancreas Biliary Center, Gastrointestinal Unit
Massachusetts General Hospital
Boston, Massachusetts, USA

Abbreviations: AGA, American Gastroenterological Association; BD-IPMNs, branch-duct intraductal papillary mucinous neoplasms; EUS-FNA, EUS-guided FNA; HRS, high-risk stigmata; ICG, international consensus guidelines; MCN, mucinous cystic neoplasms; MRI, magnetic resonance imaging; WFs, worrisome features.

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