

International guidelines for the management of pancreatic intraductal papillary mucinous neoplasms

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Abstract

The management of intraductal papillary mucinous neoplasms (IPMN) is presently evolving as a result of the improved understanding of the natural history

and biological behavior of the different pancreatic cystic neoplasms; and better preoperative diagnosis of these neoplasms due to advancement in preoperative diagnostic tools. International consensus guidelines for the management of IPMN were first formulated in 2006 and subsequently revised in 2012. Both these guidelines were constructed based on expert opinion and not on robust clinical data. The main limitation of the original Sendai guidelines was that it had a low positive predictive value resulting in many benign neoplasms being resected. Hence, these guidelines were revised in 2012. However, although the updated guidelines resulted in an improvement in the positive predictive value over the Sendai Guidelines, the results of several studies validating these guidelines demonstrated that its positive predictive value remained low. Furthermore, although both guidelines were associated with high negative predictive values, several investigators have demonstrated that some malignant IPMNs may be missed. Finally, it is imperative to emphasize that major considerations when managing a patient with IPMN including the patient's surgical risk, life-expectancy and even cost of investigations are not taken into account in current guidelines. The management of a patient with IPMN should be individualized and tailored according to a patient's risk benefit profile for resection vs surveillance.

Key words: Intraductal papillary mucinous neoplasms; Pancreatic cystic neoplasms; Cystic lesions of the pancreas; Mucinous cystic neoplasms; Pancreatic cysts; Guidelines; Management

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Core tip: Current guidelines of the management of intraductal papillary mucinous neoplasms are limited by the low positive predictive value resulting in many benign neoplasms being resected. Furthermore, despite a high negative predictive value, some malignant

neoplasms may be missed based on these guidelines.

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The incidence of pancreatic cystic neoplasms have been reported to be rapidly increasing over the past 2 decades with the routine use of cross-sectional imaging such as computed tomographic (CT) scan and ultrasonographic (US) scan^[1-3]. Many cystic lesions of the pancreas (CLP) are now incidentally detected^[1,2,4]. In the past, an aggressive resection approach was recommended for the management of cystic lesions of the pancreas detected on imaging as preoperative diagnosis was difficult and little was known of the biology and natural history of these lesions^[1,4]. However, presently; the management of pancreatic cystic neoplasms has gradually evolved in general towards a more conservative approach whereby many CLP are managed *via* surveillance rather than upfront resection^[5-10]. This may be attributed to the rapid advancement of knowledge in the field resulting in: (1) an improved understanding of the natural history and biological behavior of the different pancreatic cystic neoplasms; and (2) better preoperative diagnosis of these neoplasms as a result of a better understanding of their individual imaging characteristics and the introduction of newer diagnostic modalities such as endoscopic ultrasonography with fine needle aspirate (EUS-FNA)^[6,7,11,12]. Since the landmark papers by Compagno and Oertel in 1978^[13,14]; the general consensus among clinicians were that all mucin-containing cystic neoplasms were potentially malignant or malignant and should be resected whereas serous cystic neoplasms were benign and could be managed conservatively^[6,15,16]. Although this presumption remains true, with better understanding of the biology and natural history of these neoplasms; we now know that many mucinous lesions are relatively indolent and may take decades to transform into invasive lesions. In 1982, Ohashi provided the first pathological description of a previously unrecognized pancreatic mucinous neoplasm which we now know as intraductal papillary mucinous neoplasms (IPMN)^[17]. Based on these pioneering findings, it is widely-recognized now that mucinous neoplasms are actually composed of 2 different pathological entities termed mucinous cystic neoplasms (MCNs) and IPMNs today^[15,18,19]. Pathologically, the 2 entities may be distinguished by the presence of ovarian-type stroma in MCNs^[15,18] and communication with the pancreatic duct in IPMNs^[16]. More recently, investigators have also recognized that IPMNs could be classified according to their ductal involvement into branch-duct (BD), main-duct (MD)

and mixed-duct types (MT)^[12,20,21]. BD-IPMNs were found to exhibit a less aggressive biological behavior when compared to MD/MT-IPMN and several studies have since demonstrated that many BD-IPMNs can be managed conservatively^[2,5,8,10,20,21]. MD and MT-IPMN have been reportedly associated with a malignancy risk of between 40%-92%^[10,20-22] compared to BD-IPMN which harbors a risk of malignancy in only approximately 15%-25% of case^[10,22].

In order to guide management of MCNs and IPMNs, an international panel of experts convened in Sendai and in 2006 published consensus guidelines for the management of MCN and IPMN^[20]. These guidelines are now widely known as the Sendai Consensus Guidelines (SCG) and were formulated based on expert opinion after review of preexisting retrospective data rather than on robust clinical data^[12,23]. According to these guidelines, all MCNs and MD/MT IPMNs should be surgically resected whereas selected BD-IPMNs could be managed conservatively^[20,23]. Symptomatic BD-IPMNs or asymptomatic BD-IPMNs larger than 3 cm, with a dilated pancreatic duct > 6 mm, presence of solid component or positive cyst fluid cytology were recommended for resection according to the SCG (Table 1)^[20].

After its introduction, the SCG was widely adopted world-wide despite limited evidence supporting its utility^[23]. Subsequently, several large studies^[6,22,23] were conducted to validate the SCG. These studies revealed that the main limitation of the SCG was its low positive predictive value (PPV) whereby many benign BD-IPMNs were resected. The SCG was reported to be safe as it had a high negative predictive value (NPV) of close to 100% and malignant lesions especially invasive carcinomas were rarely missed^[8,22,23]. However, a large study from Heidelberg published in 2012 questioned the safety of the SCG as the investigators reported that in their cohort of 123 surgically-resected BD-IPMNs, 17 of 69 SCG-ve BD-IPMNs were malignant including 11 which were invasive carcinomas^[10]. Our recent systematic review^[23] of 9 studies analyzing 690 surgically resected BD-IPMNs confirmed the low PPV and high NPV of the SCG. The PPV of SCG+ve neoplasms was 150/501 (29.9%) and the NPV of SCG-ve neoplasms was 171/189 (90%). However, when the results of the study from Heidelberg were excluded, the NPV was 170/171 (99%) and none of the SCG-ve neoplasms were invasive. Recent results from the Memorial Sloan-Kettering Cancer Center and the Massachusetts General Hospital also seemed to support the findings of our systematic review whereby the Memorial group reported 5 (14%) HGD among 35 resected SCG-ve BD-IPMN^[24] and the MGH reported a 6.5% risk of HGD among 46 SCG-ve BD-IPMN smaller than 3 cm based on the revised 2012 SCG^[8,25]. No invasive cancers were detected in both these studies among the SCG-ve neoplasms^[25]. Hence, it is widely accepted by most experts that it generally safe to adopt the SCG and

Table 1 Summary of the Sendai Consensus Guidelines and Fukuoka Consensus Guidelines

Guideline	Criteria
SCG	
MD-IPMN	MPD \geq 10 mm
SCG+ve BD-IPMN	Size $>$ 3 cm
	Size \leq 3 cm with symptoms/mural nodules/ MPD dilation ($>$ 6 mm)/ positive cytology
FCG	
High risk features	Proximal lesion with obstructive jaundice Enhancing nodules Dilated main duct (\geq 10 mm)
Worrisome risk features	Size \geq 3 cm Pancreatitis Non-enhancing nodules Thickened, enhancing walls Dilated duct (5 to $<$ 10 mm) Change in duct caliber with distal atrophy Lymphadenopathy

FCG: Fukuoka; SCG: Sendai Consensus Guidelines; MPD: Main pancreatic duct; MD-IPMN: Main-duct intraductal papillary mucinous neoplasm; BD-IPMN: Branch-duct intraductal papillary mucinous neoplasm.

malignant especially invasive BD-IPMNs are rarely missed. It is difficult to determine why the data from the Heidelberg group was contrary to the results from other studies in the literature^[23-26]. The main reason is likely attributed to the fact that the investigators included lesions suspected but not pathologically confirmed as BD-IPMNs. In their study, eight of the 17 malignant IPMNs were by definition mixed type-IPMNs as there was focal tumor involvement of the main pancreatic duct^[23,25]. Furthermore, invasive preoperative modalities such as EUS and endoscopic retrograde cholangiopancreatography were rarely used by the group which could possibly have resulted in a lower sensitivity in detecting main duct involvement preoperatively^[23].

Recognizing the limitations of the original SCG, these guidelines was revised in Fukuoka and published recently in 2012^[6,9,20,21]. These revised guidelines are termed the Fukuoka Consensus Guidelines (FCG) in this report. The revisions to the SCG were made mainly to overcome its low PPV which resulted in a large number of benign BD-IPMNs being resected. The FCG now stratifies BD-IPMNs into 3 instead of 2 categories *i.e.*, high risk, worrisome risk and low risk (Table 1). According to these guidelines, most high risk lesions should be resected whereas low risk lesions may be observed. BD-IPMNs classified as worrisome risk can potentially be managed *via* surveillance after evaluation by EUS-FNA^[21]. Some of the major changes in the FCG worth highlighting are that a cyst size $>$ 3 cm or pancreatic ductal dilatation between 5 to 10 mm are now classified as worrisome risk and are no longer definitive criterion for upfront resection (with the caveat that surgically-fit patients should be considered for resection).

Like the SCG, the current FCG was formulated by

a panel of experts based on retrospective data and has not been validated. We recently performed a systematic review of 7 studies evaluating the FCG^[27]. There were 1382 patients with surgically-resected IPMNs in these 7 studies. We found that the high risk cohort according to the FCG had an improved PPV of 66% compared to the group with just worrisome features (29%). However, of concern was there were 40 of 382 (10.5%) malignant including 22 (5.8%) invasive IPMN in the FCG low risk cohort. However, just as in our earlier systematic review evaluating the original SCG^[23], we found that the overall results were again skewed by the discordant results from another large study performed by the same group from Heidelberg^[28]. This group reported 26 malignant including 18 invasive IPMN in the FCG low risk cohort. When the results from this study were excluded, there were only 14/241 (5.8%) malignant including 4/241 (1.7%) invasive FCG-ve IPMN in the remaining 6 studies.

The main limitations of most published studies to date which evaluated the SCG and FCG are that most of these studies only included surgically-resected cases^[12,23]. Hence, the "true denominator" especially for low risk neoplasms is not known. The results of these studies were likely skewed by the greater proportion of malignant neoplasms as clinicians were more likely to select patients at increased risk of malignancy based on criteria not utilized in the FCG such as age, presence of symptoms and serum tumor markers^[23,29]. Furthermore, clinicians were more likely to select more suspicious neoplasms classified as low risk for resection such as a 2.8 cm IPMN with a 4 mm main pancreatic duct as opposed to a 0.5 cm IPMN with a non-dilated duct. Hence the reported rates for PPV and NPV, were likely overestimates of the true incidence of malignancy especially for low risk tumors^[9,23]. Many consensus guidelines negative neoplasms are likely to be observed and the incidence of malignant IPMN reported in these surgical cohorts like represent the "worse case" possible.

It is important to note that both the FCG and SCG are based on "basic criteria" such as cyst size and morphology on imaging^[30]. These guidelines can potentially be refined with the addition of other criteria such as serum tumor markers which has been shown to predict malignancy in IPMN^[7,30-32]. Positron-emission tomographic scan has also been reported to be useful in distinguishing benign from malignant IPMN^[33]. In future, the use of genomic, proteomic or metabolomic analyses of cyst fluid may also prove to be invaluable in selecting BD-IPMNs for resection^[30,34,35]. Recent studies have also demonstrated the importance of the different histological subtypes of IPMN on its prognosis and these may potentially have a major impact on future genomic and proteomic studies^[36].

Finally, it is imperative to emphasize that major considerations when managing a patient with IPMN including the patient's surgical risk, life-expectancy

and even cost of investigations are not taken into account in current guidelines. The management of a patient with IPMN should be individualized and tailored according to a patient's risk benefit profile for resection vs surveillance and guidelines are precisely just guidelines^[12,25]. When considering appropriate treatment of a patient with IPMN, the risk of a patient dying from invasive cancer should be balanced against his/her risk of surgical mortality and morbidity. Today, pancreatectomy remains a surgery associated with a high morbidity^[37,38] especially for right-sided lesions although the postoperative mortality rate has fallen to about 1%-3% in top international centers^[38]. It is also important to highlight that IPMN should ideally be resected before they turn invasive as the outcome of invasive IPMN is poor with a 5-year overall survival of only 30%^[39].

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