

Comparison of the Sendai and Fukuoka Consensus Guidelines for the Management of Mucinous Cystic Lesions of the Pancreas: Are We Making Progress?

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Cystic lesions of the pancreas (CLP) are increasingly being found incidentally, due largely to the frequency of three-dimensional (3D) abdominal imaging.¹ The algorithm of resecting all solid pancreatic lesions does not apply to all cystic pancreatic lesions; observation is undoubtedly the most appropriate management for most pancreatic cysts.

The series of 317 patients with CLPs reported by Goh et al.² in this issue of *Annals of Surgical Oncology* addresses the core of these diagnostic dilemmas—which criteria should be applied to CLPs as clinicians decide which lesions warrant pancreatic resection? The authors should be recognized for their large study size, systematic review, and thorough application of two widely utilized classification systems: the 2006 Sendai Consensus Guidelines (SCG) and the revised Sendai criteria, also referred to as the Fukuoka Consensus Guidelines (FCG).^{3,4}

This comparison is critical as our understanding of CLPs evolves. The 2006 SCG were the first multidisciplinary, standardized recommendations for clinicians counseling patients on the optimal management of their pancreatic cysts, specifically designed to risk-stratify patients with intraductal papillary mucinous neoplasms (IPMNs) or mucinous cystic neoplasms (MCN). Based on these guidelines, all main duct and mixed-type IPMNs, and all MCN should be resected for a patient of appropriate operative risk. However, the Sendai criteria most prominently clarified our understanding of which side-branch (SB) IPMNs required operative intervention. An SB-IPMN associated with high-risk features

such as the presence of an intracystic mural nodule, associated main duct dilation of 10 mm, and size greater than 3 cm were considered to be of sufficient risk to warrant resection. For SB-IPMNs that did not meet these criteria, observation at specific intervals dictated by cyst size was considered safe.

Following the publication of these guidelines, the risk of dysplasia and malignancy developing in cysts less than 3 cm in size began to be more closely evaluated. In a report from the Moffitt Cancer Center, 105 patients with CLPs underwent definitive surgical therapy.⁵ The authors found that in cysts <3 cm in size, the rate of malignancy on final pathology was 34 %, and concluded that this rate of invasion was prohibitively high to recommend surveillance. At the same time, a study by Fritz et al. concurred with the Moffitt group.⁶ In this investigation, from a population of 123 resected SB-IPMNs, 69 were declared ‘Sendai negative’ (fulfilling none of the high-risk features outlined in the 2006 guidelines), and 17 (25 %) were found to have either high-grade dysplasia (HGD) or invasive ductal carcinoma within the specimen. The authors concluded that a size cutoff of 3 cm was too liberal for safe observation in patients with SB-IPMNs.

However, these studies have significant limitations. In neither of these reports are other characteristics of the IPMNs comprehensively stated—how many contained mural nodules, were cytologically positive for malignancy prior to resection, or grew over time. Any one of these features of a SB-IPMN increase the risk of that lesion harboring malignancy, and without clearly understanding the true numerators and denominators in these investigations, accurately estimating the risk of malignancy is not possible—we do not know how many lesions were truly ‘Sendai negative’. In particular, the study from Moffitt was unique in that the authors utilized endoscopic ultrasound (EUS) to evaluate the patients in their series, which implies that only cysts with high-risk features were being resected.

In 2012, the 2006 SCG were revised in Fukuoka, Japan, in an attempt to refine recommendations for operative intervention for IPMNs.⁴ The salient features of the FCG included updates for both main-duct and SB-IPMNs, introducing dichotomized risk strata—‘high risk’ and ‘worrisome’ features. For main-duct (MD) IPMNs, FCG recommended viewing lesions with 5–9 mm pancreatic duct dilation as ‘worrisome’ but not necessitating removal. However, the revision of SB-IPMN criteria were more sophisticated. ‘High-risk’ features included associated MD dilation >10 mm, jaundice resulting from a cystic lesion in the head, or an enhancing solid nodule within the cyst; the recommendation was that all high-risk lesions should be resected. ‘Worrisome’ features of CLPs, but those not necessarily requiring immediate pancreatectomy, included symptomatic pancreatitis, cyst size >3 cm, thickened/enhancing cyst walls, MD dilation of 5–9 mm, a non-enhancing mural nodule, or an abrupt change in caliber of the pancreatic duct. Although many of these recommended changes were subtle, the most significant was the classification of a side branch IPMN >3 cm as only worrisome, and not requiring immediate resection. For many practitioners who had reliably used that size cutoff for definitive surgical decision making, this was a significant paradigm shift.

This de-emphasis on size is primarily supported by data from the largest published series of SB-IPMNs from the Massachusetts General Hospital.¹ In this series of 563 patients, 240 of whom underwent resection, subset analysis revealed that only 6.5 % of SB-IPMNs <3 cm had HGD in the final specimen. When lesions over 3 cm were considered, that rate increased to only 8.8 %, although one case of invasive carcinoma was found. Importantly, CLPs >3 cm with either HGD or invasive carcinoma almost always possessed other ‘worrisome’ or ‘high-risk’ features according to the revised Sendai criteria.

The study by Goh et al.² in this month’s edition of *Annals of Surgical Oncology* corroborates many of the findings presented by the Boston group. In applying both the original SCG and also the revised Sendai guidelines of 2012 to 317 patients, all of whom underwent surgical extirpation of the CLPs, the authors found that the revised FCG have superior positive and negative predictive values for preliminary malignant/malignant lesions (88 and 92.5 %, respectively) compared with the SCG (67 and 88 %, respectively). However, this report has notable methodologic concerns that impact its conclusions. Firstly, this is a retrospective review of a very heterogeneous population—IPMNs comprised only 21 % of all CLPs in this series—with a substantial percentage of other mucinous and non-mucinous cysts included in the analysis; previous studies have demonstrated the Sendai criteria to be inaccurate when used to evaluate non-mucinous cysts.⁷ Furthermore, the institution reporting these results changed

their surgical approach in 2006, from a policy of universal resection to one of selective observation based on the Sendai criteria. This practice of standard resection prior to 2006 certainly could have resulted in a higher negative predictive value by lowering the denominator.

The issue of EUS application deserves special comment. Neither the initial SCG nor the revised Sendai criteria consistently utilized EUS in cyst evaluation or treatment planning, and while there are good reasons for this—lack of ubiquitous EUS availability and expertise, as well as significant inter-endoscopist variability—not utilizing this often-helpful diagnostic modality is problematic. Perhaps most importantly, EUS can help to differentiate a mucinous lesion (MCN, IPMN) from non-mucinous cysts—a critical decision point in the diagnostic and treatment algorithms for CLP. Furthermore, while not every CLP requires EUS—a classic IPMN with a clear operative indication probably does not require yet another invasive test—endoscopic cyst characterization and cyst aspirate cytology/carcinoembryonic antigen (CEA)/amylase levels can be invaluable.

To date, our algorithm for IPMNs at the University of Cincinnati has largely followed the original Sendai recommendations. In appropriate-risk individuals, all main-duct IPMNs are resected, while a more selective approach is reserved for SB-IPMNs. SB-IPMNs >3 cm undergo resection, while those <3 cm without worrisome cytologic aspirate or mural nodules are closely observed (we liberally use EUS for lesions that do not have a classic appearance on 3D imaging).

However, as we continue to refine our evaluation of IPMNs, other non-Sendai criteria also impact our medical decision making. Cyst CEA levels, both initial and their rate of rise over time, strongly influence our comfort with observation, and we tend to be more aggressive with CLPs with a rising CEA level (although admittedly the data to support this strategy are not as strong as for other cyst features). Furthermore, and in line with many other expert centers, cysts that grow at a rate of 2 mm/year or more are of sufficient concern for us to recommend resection; we believe size change should be considered in the development of future consensus guidelines.⁸

In summary, the experience of Gho and colleagues adds further substantiating data that the revised Sendai criteria are currently the most appropriate widespread recommendations to adopt at a population level. However, with elimination of cyst size as an absolute criterion for resection of SB-IPMNs must come heightened awareness that a small population of patients will have large, low-risk cysts that may harbor HGD or even invasive malignancy. Cyst growth, CEA levels, and other patient-specific variables should continue to factor into our patient counseling, filling in around the framework of the thoughtful, and increasingly studied, revised Sendai classification.

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