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Retrospective application of 2012 revised international consensus guidelines to suspected mucinous-type pancreatic cysts managed in the sendai era

Abstract

Background: Pancreatic cystic lesions (PCL) are a common clinical problem. International consensus guidelines were published in 2006 and revised in 2012 to assist clinicians in the diagnosis and management.

Methods: 2012 international consensus guidelines (ICG-2012) were retrospectively applied to PCLs originally managed with ICG-2006. PCLs diagnosed in 2008-2012 (Sendai era) were included if: (1) lesions were suspected to be BD-IPMN (branch duct intraductal papillary mucinous neoplasm) prior to surgery with carcinoembryonic antigen < 192, (2) required resection based on ICG-2006, (3) final diagnosis verified by histopathology. Performance of ICG-2012 was tested with indications for resection defined as carcinoma and pre-malignant lesions such as pancreatic intraepithelial neoplasia (PanIN).

Results: 15 PCLs met the inclusion criteria. Applying ICG-2012, following were the sensitivity, specificity, negative predictive value, positive predictive value, and accuracy, expressed as % (N/C = not calculable), for each of the criteria featured in the proposed algorithm. High-risk stigmata: enhancing solid component within cyst (50, 92, 92, 50, 87), main pancreatic duct (MPD) ≥ 10mm (0, 100, 87, N/C, 87). Clinical worrisome features: pancreatitis (0, 85, 85, 0, 73). Worrisome features on cross sectional imaging: cyst ≥ 3cm (0, 38, 71, 0, 33), thickened/enhancing cyst walls (0, 85, 85, 0, 73), MPD 5-9 mm (33, 100, 87, 100, 88), non-enhancing mural nodule (0, 92, 86, 0, 80), abrupt change in PD caliber with distal atrophy (100, 100, 100, 100, 100). EUS (endoscopic ultrasound) features: definite mural nodule (100, 62, 100, 29, 67), MPD suspicious for involvement (0, 100, 87, N/C, 87), cytology (0, 100, 92, N/C, 92).

Channeling PCLs through the ICG-2012 algorithm, 4 lesions [1 adenocarcinoma and 3 mucinous cystic neoplasms/MCNs (if the resection indication was expanded to include MCNs)] that met resection criteria with ICG-2006 would not be resected utilizing ICG-2012.

Conclusion: Feature in ICG-2012 algorithm that predicted carcinoma/pre-malignant lesions with highest accuracy was abrupt change in PD caliber with distal atrophy on cross sectional imaging. Cyst details such as mural nodules may be missed on cross sectional imaging but detected on EUS, which suggests a possible need for at least one EUS in PCL size of 1-2 cm.

Keywords: pancreatic cystic lesion, endoscopic ultrasound, intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, pancreatic cancer, carcinoembryonic antigen,,k practice guidelines

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Abbreviations: CEA, carcinoembryonic antigen; EUS, endoscopic ultrasound; ICG, international consensus guidelines; IPMN, intraductal papillary mucinous neoplasms; IQR, interquartile ranges; MCN, mucinous cystic neoplasms; MRCP, magnetic resonance cholangiopancreatography; NPV, negative predictive value; PCL, pancreatic cystic lesions; PanIN, pancreatic intraepithelial neoplasia; PPV, positive predictive value; SPPN, solid pseudopapillary neoplasms

Background

Pancreatic cystic lesions (PCL) have become an increasingly common challenging clinical entity for primary care physicians, gastroenterologists, radiologists and surgeons. This is in part due to a rise in incidental discovery of pancreatic cysts, which is attributed to increased use of cross sectional imaging. The reported prevalence for asymptomatic PCLs is 2.5% based on studies that used computed tomography (CT) as the imaging modality and increases to approximately 20% if magnetic resonance imaging (MRI) was used.[1,2] Heterogeneous nature of PCLs further complicates management of these lesions. Commonly encountered PCLs are serous cystadenoma, mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), solid pseudopapillary neoplasms (SPPN), and cystic neuroendocrine neoplasms.[3] Among these lesions there are benign, premalignant with varying potential for progression to malignancy, and malignant lesions with cystic degeneration.

The management of PCLs has undergone revolutionary changes. It was originally believed that all mucinous cysts must be surgically excised and serous neoplasms can be closely monitored.[4] However, improved understanding of the histopathologic features, imaging characteristics and natural history of these lesions allowed surveillance of certain mucinous neoplasms. This underscored the importance of preoperative distinction between lesions that are frankly malignant or have high potential for malignancy from those that have a more benign natural course. Therefore, clinical guidelines have been developed to aid in the selection of patients for the most appropriate management approach.[5,6]

The first of such guidelines, international consensus guidelines for management of IPMNs and MCNs of the pancreas, referred to as ICG-2006 in this article but also known as the Sendai consensus guidelines, was published in 2006 by a panel of experts.[5] These guidelines risk stratify PCLs based on size and presence of high-risk features such as presence of symptoms, solid component/mural nodules, and dilated main duct (≥5 mm). ICG-2006 stated that all PCLs ≥ 3cm suspected to be branch duct IPMNs and those with high risk features should be resected. ICG-2006 attracted considerable attention in the scientific society and was validated in several studies. It was shown to have high sensitivity and negative predictive value but low specificity and positive predictive value.[7–10] In 2012, an expert panel gathered in Fukuoka, Japan, and published revised guidelines for management of MCNs and IPMNs.[6] Both guidelines agree on resection of all MCNs and main duct IPMNs (MD-IPMN) in surgically fit patients; however, the new guidelines differ from the previous version mainly in the addition of the new concepts of "high-risk stigmata" and "worrisome features" and the indications for endoscopic ultrasound (EUS). The ICG-2012 or 'Fukuoka' guidelines do not recommend EUS for cysts < 2cm. There is paucity of studies to date which evaluate both the Sendai and Fukuoka guidelines for management of PCLs. The present study was performed to evaluate the performance of Fukuoka guidelines retrospectively applied to patients with PCLs who were managed in the 'Sendai' era.

Methods

Data was searched retrospectively for PCLs diagnosed 2008-2012. Inclusion criteria were as follows: (1) lesions which had CEA (carcinoembryonic antigen) < 192 and were suspected to be BD-IPMN (branch duct intraductal papillary mucinous neoplasm) prior to surgery, (2) Met the criteria for surgical resection based on ICG-2006, (3) final diagnosis verified with histopathology. All patients had at least one form of cross-sectional imaging such CT and MRI/MRCP (magnetic resonance cholangiopancreatography). Prior to the introduction of ICG-2012, there was no institution-wide protocol for the evaluation of cystic pancreatic neoplasms at our medical center with regards to the use of cross sectional imaging. Cross sectional imaging were performed for various reasons, both gastrointestinal (GI) and non-GI indications. Patients that were found to have PCLs on these imaging studies were then referred to gastroenterology at the discretion of the clinician ordering the cross sectional imaging for further work-up. All but one patient also had EUS at which time, CEA and amylase levels in cystic fluid were obtained when feasible. Lesions that had obvious mass external to the cysts on cross sectional imaging were excluded. Morphological features of lesions such as cyst location, cyst size, diameter of the main pancreatic duct, presence of septation(s) and mural nodule were evaluated. Communication between the PCL and the pancreatic duct on the cross sectional imaging, suggesting BD-IPMN as the etiology, was determined by the radiologist reading the particular study although this was not always possible. Similarly, communication with the pancreatic duct was noted on EUS when clearly visualized.

Clinical presentation and demographic data were obtained from electronic medical record. We then retrospectively tested the performance of ICG-2012 guidelines for identifying patients who needed surgical resection, with indications for resection defined as carcinoma and pre-malignant lesions such as pancreatic intraepithelial neoplasia (PanIN). The study was approved by the Kaiser Permanente Southern California institutional review board.

Statistics

Analyses were performed using Stata version 10 (College Station, TX). Patient characteristics are described as median and interquartile ranges (IQR). Performance of ICG-2012 was tested by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each of the resection criteria.

Results and discussion

15 patients met the inclusion criteria. The median age was 58 years (25-75% interquartile range 50-65). There were 10 females (67%) and 5 males (33%) (Table 1). Majority of the lesions were in the pancreatic tail (9/15, 60%); the remainder were in the pancreatic body (4/15, 27%), uncinate process (1/15, 7%), and head (1/15, 7%). The median cyst size of all PCLs was 3.7 cm (25-75% interquartile range 1.9-4.4) on cross sectional imaging. The prevailing indications for surgery based on ICG-2006 criteria were the presence of nodules followed by the cyst size.

Table 1 Clinicopathologic characteristics of patients with pancreatic cystic lesions

Age [median, (25-75% interquartile range)]	**58 (50-65)**
Gender [n, (%)]	
Male	5 (33)
Female	10 (67)
Symptoms/presentation [n, (%)] §	
Abdominal pain/discomfort	11 (73)
Pancreatitis	2 (13)
Fatigue	1 (7)
Weight loss	3 (20)
Nausea +/- vomiting	5 (33)
Decreased appetite	1 (7)
Diarrhea	1 (7)
Tobacco use [n, (%)] ‡	
Yes	8 (53)
No	5 (33)
Family history of pancreatic cancer [n, (%)] ‡	
Yes	1 (7)
No	12 (80)
Cyst location [n, (%)]	
Tail	9 (60%)
Body	4 (27%)
Head	1 (7%)

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Table Continued...

Age [median, (25-75% interquartile range)]	**58 (50-65)**
Uncinate process	1 (7%)
Pathology [n, (%)]	
MCN	7 (47)
MCN with PanIN 1B	1 (7)
IPMN with pancreatitis	1 (7)
Adenocarcinoma	1 (7)
Neuroendocrine tumor	2 (13)
Solid pseudopapillary tumor	1 (7)
Pseudocyst	2 (13)

MCN, mucinous cystic neoplasm; IPMN, intraductal papillary mucinous neoplasms; PanIN, pancreatic intraepithelial neoplasia

§ Some patients had more than one symptoms

‡ Data only available in 13 patients.

Final histopathologic diagnoses were MCN (7/15, 47%), adenocarcinoma (1/15, 7%), pseudocyst (2/15, 13%), well-differentiated neuroendocrine tumor (2/15, 13%), solid pseudopapillary tumor (1/15, 7%), MCN with PanIN-IB (1/15, 7%), and IPMN (1/15, 7%).

Table 2 summarizes the sensitivity, specificity, NPV, PPV, and accuracy, for each of the criteria featured in the proposed algorithm in ICG-2012.The ICG-2012 criterion that predicted carcinoma and/or pre-malignant lesions with highest accuracy was abrupt change in PD caliber with distal atrophy (accuracy 100 %) on cross sectional imaging (Table 2). In 6 cases where mural nodules were detected on EUS, they were not seen on initial cross sectional imaging.

When PCLs diagnosed and treated in the ICG-2006 era were filtered through ICG-2012 algorithm, 4 lesions that met the old resection criteria would not have been resected utilizing the new criteria. They were adenocarcinoma (1/4) and MCNs (3/4), if the resection indication was expanded to include MCNs. None of these cases had concerning symptoms listed in ICG-2012, i.e. obstructive jaundice and pancreatitis, that would have led to further work-up with EUS solely based on ICG-2012. Also, none of these patients had a follow-up MRI/MRCP after the initial diagnoses made with CT. The characteristics of these lesions are shown in Table 3.

In the time period between the retrospective review of the cases used for this particular study and the manuscript preparation, there have been two known cases where the 'cystic neoplasms' of the pancreas on cross sectional imaging below the size criteria for further immediate investigation resulted in referrals for EUS, not in accordance with ICG-2012, and eventual diagnosis of malignancy. One case was a 68 year old female who had a 10 mm pancreatic tail cyst seen on CT urogram, which was followed up with MRI of the pancreas. MRI was read as having a 10 mm cystic non-enhancing lesion in the tail of the pancreas with tiny extensions suggesting it may connect with small pancreatic duct branches suspicious for IPMN. However, the gastroenterologist had high enough index of suspicion to refer the patient for EUS, which found malignant mass adjacent to the lesion that was not seen on cross sectional imaging. The second case was a 57 year old female who had a 1 cm cystic lesion in pancreatic tail on CT. Patient then had a repeat CT 5 months later by the primary care physician, which was not in accordance with the regional health system guideline that was developed based on ICG-2012. This latter CT showed unchanged cystic lesion but also mild acute pancreatitis versus neoplasm nearby in the tail. On EUS, patient was found to have a mass lesion, FNA of which was positive for neuroendocrine tumor.

Given the result of our study and experience with lesions that would have been missed if ICG-2012 was strictly followed, it may be reasonable to suggest at least one EUS be performed for cyst sizes 1 to 2 cm. This suggestion becomes more reasonable when we consider that in 6 of our patients, mural nodules were seen only on EUS and not on cross sectional imaging. Additionally, EUS has been shown to be superior to a combination of CT and MRI in detecting pancreatic adenocarcinoma. CT combined with MRI was shown to detect pancreatic adenocarcinoma in only 43% of patients who were diagnosed with EUS.[11] In a recent paper, Farrell and Fernandez-Del-Castillo underscore the usefulness of EUS for cystic lesions of 1 to 3 cm in size that do not possess high-risk stigmata on cross sectional imaging since it can be used to rule out associated masses, discover nodules, obtain cyst fluid sample for cytology and CEA measurement and help differentiate serous from mucinous cysts.[12] To investigate the role of cross sectional imaging and EUS in evaluating small pancreatic cysts, we searched the literature published between 2005 and 2015 using the keywords "pancreatic cystic lesion" and "MRI" or "CT" or "EUS" in Medline. From the initial 254 articles that were reviewed for relevance, 146 were excluded. The remaining 108 abstracts were reviewed to include studies that addressed small cyst sizes and simultaneous use of EUS and a cross sectional imaging modality. Two articles met the criteria and the results are summarized in Table 4.[13,14]

Table 2 Performance of individual ICG-2012 criteria

Criteria in ICG-2012		**Sensitivity**	**Specificity**	**NPV**	**PPV**	**Accuracy**
High-risk stigmata	Enhancing Solid component	50	92	92	50	87
	MPD ≥10 mm	0	100	87	N/C	87
Clinical worrisome features	Pancreatitis	0	85	85	0	73
	Cyst ≥ 3 cm	0	38	71	0	33
Worrisome features on cross sectional imaging	Thickened/enhancing cyst walls	0	85	85	0	73
	MPD 5-9 mm	33	100	87	100	88
	Non-enhancing mural nodule	0	92	86	0	80
	Abrupt change in PD caliber with distal atrophy	100	100	100	100	100
	Definite mural nodule	100	62	100	29	67
EUS features	MPD suspicious for involvement	0	100	87	N/C	87
	Positive cytology	0	100	92	N/C	92

ICG, international consensus guidelines; NPV, negative predictive value; PPV, positive predictive value; MPD; main pancreatic duct; PD, pancreatic duct; EUS, endoscopic ultrasound; N/C, not calculable

Table 3 Characteristics of lesions that met the ICG-2006 resection criteria but not the ICG-2012 criteria

Age/Gender	High risk stigmata	Worrisome features	Cyst size on CT (cm)	Cyst location	EUS features	Final diagnosis
23/F	No	No	1.5	Tail	Nodule	MCN
58/F	No	No	2.0	Body	Nodule	MCN
79/F	No	No	1.8	Tail	Nodule	MCN
71/M	No	No	2.0	Head	Nodule	Adenocarcinoma

F, female; M, male; CT, computed tomography; EUS, endoscopic ultrasound; MCN, mucinous cystic neoplasm

Table 4 Review of literature on the role of combined cross sectional imaging and EUS in management of small pancreatic cysts

Study	N	Cyst Size §		Proportion of Patients with Imaging Performed			Sensitivity for Malignancy			Incremental Diagnostic Yield of EUS over CSI
		Small	Large	CT	MRI	EUS	EUS	CSI	EUS+CSI	
Khashab et al. [14]	154	71% ‡	29%	90%	34%	100%	49% (59%*)	CT-11% (5%*) MRI-0%	59.1% **	CT-36% MRI-54%
De Jong et al. [13]	32	6%	94%	N/A	100%	100%	25%	50%	75%	N/A

CSI, cross sectional imaging; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound

§Definition of small and large cyst sizes are different in the two studies: Khashab et al. [14] (<3 vs ≥3) and De Jong et al. [13] (<2 vs ≥2)

‡ Khashab et al. [14] further divides small cysts into three sizes: < 1cm (15.64% of patients), 1-2 cm (39.3%), 2-2.99 cm (15.84%). However, data analysis is not performed based on these sub-divisions.

*Sensitivity for malignancy in small cysts

**Combination of EUS + CT equally sensitive to EUS + MRI

One of the limitations of our study is the small number of patients, which is due to the fact that the data was from a community hospital. The number of pancreatobiliary surgeries at our center in years 2013 and 2014 were 42 and 27, respectively. In addition, final histopathologic diagnosis of included patients were heterogeneous as seen above, and we did not strictly include only those patients who were confirmed to have branch duct-IPMN, primary entity that the international consensus guideline algorithms are designed for. However, one needs to keep in mind that it can be very difficult to differentiate the different types of pancreatic cystic lesions prior to histopathologic verification, particularly between IPMN and MCN. This is the reason for the emergence of recent studies and abstracts looking at biomarkers such as k-ras, GNAS and mRNA that can aid in the correct diagnosis of these cystic lesions.[15] Thus, our study reflects the reality of the PCL conundrum that gastroenterologists face. Lastly, it is peculiar that our analysis showed MPD diameter of 5-9 mm having nearly the same accuracy in predicting carcinoma and/or pre-malignant lesions as MPD ≥10mm. While the exact reason is unknown, it is probably partly related to the small sample size. Regardless, it points to the fact that even MPD dilation to 5-9 mm can be an important parameter that should not be overlooked.

Conclusion

In conclusion, PCLs are common findings on cross sectional imaging that pose a difficult diagnostic challenge. This coupled with the fact that some PCLs are precursors of pancreatic malignancy caused a heightened interest in these entities including the birth and revision of the international consensus guidelines. Older version, 'Sendai guidelines,' had high sensitivity and negative predictive value but low specificity and positive predictive value. The revision, 'Fukuoka guidelines,' may be more specific in the diagnosis of malignant cystic lesion, but may have shortcomings as noted above. More studies that test the performance of the Fukuoka guidelines are needed.

Authors' contributions

Armen Eskandari: data abstraction, data analysis, manuscript preparation

Charles T Chaya: study design, data abstraction, data analysis, manuscript review

Albert Ko: study design, data analysis, manuscript review

Brian Lim: study design, data abstraction, data analysis, manuscript preparation, manuscript review.

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Conflicts of interest

The authors declare no conflict of interest.

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