Guidelines on Pancreatic Cystic Neoplasms: Major Inconsistencies With Available Evidence and Clinical Practice—Results From an International Survey

Epidemiologic studies have estimated that between 2% and 45% of the general population harbor a pancreatic cyst.[1] Pancreatic cystic neoplasms (PCNs) encompass a wide spectrum, from benign entities to premalignant conditions.[2] Surgery offers the possibility of preventing pancreatic cancer or its treatment during an early stage; poor patient selection can expose many individuals to the severe sequelae of a major pancreatic resection.[3]

Despite the efforts of clinical and basic research and several thousands of published studies, management of PCNs remains controversial and is driven by 3 main sets of guidelines: the International Guidelines of the International Association of Pancreatology (IAP)[4] published in 2006 and updated in 2012 and 2016, the European evidence-based guidelines[5] published in 2013 and updated in 2017, and the guidelines of the American Gastroenterological Association (AGA)[6] published in 2015. These guidelines share some key points, but also have profound differences with respect to patient management. Moreover, they are primarily based on expert opinions or weak scientific evidence stemming from studies burdened by important selection biases. Little is known about the level of circulation and application of the guidelines in clinical practice. Before further updating any of the existing guidelines, it is mandatory to identify and solve these discrepancies by focusing the efforts of the pancreatic community on specific low-evidence areas.

The aim of the present study was to assess the dissemination, clinical application, and the perceived reliability of the 3 main sets of guidelines for the management of PCNs based on the available evidence.

Methods

This project was promoted by the University of Verona Hospital Trust and approved by the Institutional Review Board (approval number 2390CESC, Verona Ethical Committee). Support was engendered from the United European Gastroenterology Society and the European Digestive Surgery Society. We designed a mobile application (iCyst) to disseminate guidelines on PCN management. The app was released on October 2019 and consisted of 2 different sections: a guidelines consultation section where flowcharts of the 3 guidelines can be virtually browsed, and a patient simulation section where the user can simulate a case and obtain the recommendations of the 3 different guidelines based on the clinical and radiologic features. The patient simulation section could be unlocked after completing an online survey about the current application of guidelines for the management of PCNs. Both the survey and the iCyst app were promoted through United European Gastroenterology Society, European Digestive Surgery Society, and major social media. The method of disseminating the survey was specifically designed to obtain a real-world picture of the management of PCNs that is not limited to experts in this field.

The 47 questions of the survey were designed to be completed in 12 minutes. The survey was closed after 12 months on September 2020. Only responders with a verified email address were included in the final analysis.

PCN classification and definitions of clinical and radiologic features were all derived from the IAP,[4] European evidence-based,[5] and AGA[6] guidelines.

Statistical Analysis

Data were processed and analyzed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and IBM SPSS Statistics (version 24 for Mac, Armonk, NY). All data are reported as frequencies and percentage. Subgroup analysis were performed to compare answers provided by different categories of responders using the χ^2 or Fisher exact tests.

Results

Demographics and Experience with PCNs

The survey was completed by 259 international responders. Most responders were from Europe (86%), followed by Asia (8%), and the United States (6%), and practiced in university or teaching hospitals (85%) evaluating >100 patients per year with pancreatic diseases (79% of cases). Only 23% declared evaluating <25 patients per year affected by PCNs, and 47% had <5 years of experience in managing PCNs. Most responders were either surgeons (58%) or gastroenterologists (38%). The best-known guidelines were the European (79%) followed by IAP (69%) and AGA (61%) guidelines. Interestingly, 7% of responders claimed not to be aware of any guidelines. Most diagnostic techniques, including magnetic resonance imaging (MRI), computed tomography scans, endoscopic ultrasound (EUS) examination, and cyst fluid analysis were available for all responders; however, only 41% had access to contrast-enhanced EUS examination.

Case Vignettes and Clinical Practice

The full text of the case vignettes and distribution of answers are displayed in Table 1.

Dilatation of the Main Pancreatic Duct Alone. The first case was a young patient without comorbidities presenting with a dilated main pancreatic duct of 9 mm as the sole radiologic feature. European guidelines would have suggested surgery, IAP additional evaluation with EUS, and AGA an MRI in 6 months. However, only 11% of responders recommended surgery, whereas 57% recommended EUS and 26% short-term surveillance in 3–6 months.

Isolated Large Branch Duct Intraductal Papillary Mucinous

Table 1. Case Vignettes and Clinical Practice

Questions	Answers	*n* (%)
What would you suggest in this case? A 55-year-old man, no relevant comorbidities, chronic diarrhea, first observation, main pancreatic duct 9 mm, no nodules or solid components, no lymphadenopathies.	Surgery	28 (11)
	3/6 months follow-up with MRI	**68 (26)**
	12 months follow-up with MRI	11 (4)
	Additional evaluation with EUS	**147 (57)**
	None of the previous mentioned	3 (1)
What would you suggest in this case? A 65-year-old man, fit for surgery, first observation, 54 mm cyst in the head, clear connection with the ductal system, no additional features, no symptoms.	Surgery	**89 (34)**
	3/6 months follow-up with MRI	24 (9)
	Close surveillance alternating MRI with EUS every 3–6 months	34 (13) **108 (42)**
	Additional evaluation with EUS	1 (0.3)
	None of the previous mentioned	
Suppose that after completing the workup the cyst remained stable for 12 months, what would you suggest?	I still strongly consider surgery	**89 (34)**
	I suggest close surveillance alternating MRI with EUS every 3/6 months	**80 (31)** **84 (32)**
	Follow-up with MRI after additional 12 months	2 (0.7)
	None of the previous mentioned	
What would you do in this case? A 67-year-old woman, occasional finding of multifocal (largest cyst 15 mm) IPMN with no additional features.	Surgery	9 (3)
	Surveillance with MRI at 6 months, then after additional 12 months if stable.	**192 (74)** 46 (18)
	Additional evaluation with EUS	5 (2)
	Surveillance with ultrasounds	6 (2)
	None of the previous mentioned	
Supposing you chose follow-up, 5 years after no changes occurred in cyst's features, what would you suggest?	Surgery	7 (3)
	Surveillance with MRI every 12 months	**93 (36)**
	Surveillance with MRI at interval >12 months	**94 (36)**
	Surveillance with ultrasounds	16 (6)
	Stop follow-up	**46 (18)**
Which cyst-related symptoms do you consider as indication for surgery? (Multiple answers allowed)	Acute pancreatitis	99 (38)
	Recurrent acute pancreatitis, no other causes	**199 (77)**
	Jaundice	**231 (89)**
	Abdominal discomfort	47 (18)
	Dyspepsia	20 (8)
	Back pain	41 (16)
	None of the previous mentioned	4 (2)
	No	91 (35)
Do you know the implications of all the different epithelial subtype of IPMNs and of the differentiation of the invasive component?	Yes	**127 (49)**
	No	109 (42)
Do you think that distinguishing the epithelial subtype and the differentiation of the invasive component could be of clinical importance?	Yes	**205 (79)**
	No	29 (11)
	EUS	100 (39)
	CT scan	36 (14)
	MRI without contrast enhancement (only MRCP)	37 (14)
	MRI with contrast enhancement and MRCP	218 (84)

CT, computed tomography; EUS, endoscopic ultrasound; IPMN, Intraductal Papillary Mucinous Neoplasms; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

Neoplasms. The second case was a young man without comorbidities presenting with a presumed branch duct (BD)-intraductal papillary mucinous neoplasm (IPMN) of 54 mm as the sole radiologic feature. In this case, most responders (42%) would have followed the IAP guidelines, suggesting EUS examination, and 34% would have suggested surgery. If the same case had remained stable for 12 months, the responders were split equally among 3 discrete positions: surgery (34%), short-term surveillance (31%), and long-term surveillance (32%).

Multifocal BD IPMN. In the case of a 67-year-old woman without comorbidities presenting with a multifocal presumed BD-IPMN <15 mm, 74% of physicians would have

suggested surveillance with MRI and, in case of stability for 5 years, 72% would have continued versus 18% discontinued surveillance.

Presence of Symptoms. Physicians were then questioned about the role of symptoms in PCN with multiple answers allowed. A strong agreement to suggest surgery in cases of symptoms was encountered only in case of jaundice (89%) and recurrent acute pancreatitis (77%). Only a few responders would have suggested surgery in the presence of abdominal discomfort (18%), dyspepsia (8%), and back pain (16%).

Guidelines Awareness and Available Evidence

Most responders followed the European guidelines (41%) in their practice, followed by IAP guidelines (36%), and AGA (10%) guidelines.

Surgical Indications. There was a strong agreement (97%) in suggesting surgery for high-risk stigmata, as suggested by the IAP guidelines. However, there was a strong disagreement on worrisome features; 68% would suggest surgery and 27% an additional workup. In the presence of $\geq$1 relative indication for surgery according to the European guidelines, 36% would have suggested resection only in patients without comorbidities, and 26% would have suggested surgery regardless of their presence. Despite the relevant tendency to choose surgery in the presence of worrisome features/relative indications, approximately 80% of responders would consider surveillance as safe in case of an main pancreatic duct of 5.0–9.9 mm or a cyst size of >30 mm once present as a unique radiologic feature.

According to 67% of responders, there was enough evidence to support surgery in the presence of mural nodules, to 82% in case of main pancreatic duct $\geq$10 mm, to 18% in case of main pancreatic duct 5.0–9.9 mm, to 38% based only on cyst size, to 15% based only on Ca19.9 levels and to 38% based only on cyst growth rate. In the presence of an invasive component on the final pathology, 68% would suggest adjuvant chemotherapy, even if only 31% believed that this choice was supported by evidence.

Surveillance Strategies. Regarding nonoperatively managed PCNs, only 18% would consider surveillance discontinuation after 5 years of surveillance, in accord with the AGA guidelines. At the same time, 54% believed that there was not enough evidence to recommend lifetime follow-up in case of IPMN without indication for surgery. Moreover, 64% of responders believed that there was not enough evidence to recognize that lifetime follow-up is associated with lower mortality for pancreatic cancer. Regarding the imaging technique for follow-up/surveillance, there was strong agreement (84%) for MRI with cholangiopancreatography, whereas only 6% believed that transabdominal ultrasound examination can be used.

Intraoperative Strategies. There was strong agreement on the use of frozen sections; 83% supported their routine use. However, there was worrying disagreement regarding how to proceed based on the results. Only 51% believed that an additional resection was not required in case of low-grade dysplasia. In the presence of high-grade dysplasia, 66% would proceed with an additional resection, but 27% would directly proceed to total pancreatectomy. In the presence of a denuded epithelium preventing a proper pathological assessment, 57% would proceed with an additional resection, whereas 34% believed that an additional resection is usually not required.

Interestingly, 30% of responders would agree to operate on a patient asking for surgery because they were worried about an IPMN, even if it was deemed low risk.

Pathological Aspects. Regarding pathological assessment, only 56% usually distinguished between pancreatic cancer arising from an IPMN and a concomitant pancreatic cancer. Moreover, only 49% recognized the implications of the different IPMN epithelial subtypes and invasive component types; of note, 79% believed that knowing these data could be of clinical importance.

Discussion

Despite this survey not being limited to expert pancreatologists, the primary characteristics of responders revealed that most PCNs are still handled by physicians working at university or teaching hospitals with a high volume of pancreatic diseases. This evidence suggests that PCNs are treated as a rare disease, despite several studies demonstrating a high prevalence in the general population, especially among the elderly.[1,7,8] Outside the community of pancreatologists, patients are then at higher risk for treatment disparities. Therefore, experts have a duty to improve awareness about PCN and related guidelines in nonspecialist physicians.

Guidelines have an adequate level of dissemination among surgeons and gastroenterologists. However, major concerns regarding their actual application in clinical practice immediately emerge due to resource availability. More than half of physicians do not have access to contrast-enhanced EUS examination, preventing the proper application of guidelines in clinical practice. This evidence could represent the tip of the iceberg, because accurate data about the availability of imaging techniques in scenarios other than those explored by the survey are limited. Guidelines should be disseminated to include most of the medical community and should be easily applicable in any health care system to avoid treatment disparities.

Through case vignettes and direct and indirect questioning, we identified several low-evidence areas that are likely primarily responsible for the discrepancies between guidelines and clinical practice.

Enhancing mural nodules $\geq$5 mm are considered high-risk stigmata and an absolute indication for surgical resection.[4,5] However, >30% of physicians who answered this survey did not believe that there is enough evidence to suggest surgery once present. Mural nodules predict malignancy in surgical series,[9] but some questions remain unsolved, including their role in patients under surveillance, the correlation between radiologic, and final pathological examination, the

optimal size cutoff to best scale the risk of malignancy, and the most accurate imaging technique to obtain optimal characterization.[10,11]

Despite there being several lines of evidence showing an increased rate of malignancy in resected IPMNs with main pancreatic duct between 5.0 and 9.9 mm,[12–14] this issue still raises many doubts, because >80% of responders believe that there is not enough evidence to suggest surgery based on a moderately dilated main pancreatic duct. The available evidence is not considered adequate, probably because it was retrieved by sole surgical series. Overall, it seems that the presence of a moderate main pancreatic duct dilatation alone does not cause an increased perception of cancer risk among clinicians until prospective observational data on the surveilled cyst become available.

Similar concerns can be identified when dealing with cyst size and cyst growth rate, because the available evidence rarely considers their role outside of a surgical series.[15–17] Indeed, >60% of responders stated that there is not enough evidence to suggest surgery based on these 2 features.

Another important issue involves symptoms. Several guidelines strongly recommend surgery in case of symptoms, but rarely define what constitutes a "symptom." Apart from a few pancreas-specific signs and symptoms, such as jaundice or severe abdominal pain consistent with acute pancreatitis, patients affected by PCNs usually report many complaints, which are to be considered concomitant to the PCN rather than determined by it.[18–20] Further studies are needed, and guidelines should be more detailed in identifying which patients actually require surgery for the presence of PCN-related symptoms to avoid unnecessary surgery.

One of the most vital issues identified likely concerns surveillance discontinuation. For the first time, the AGA guidelines[6] proposed ceasing surveillance after 5 years in patients with a stable PCN. This recommendation caused perplexity, if not open rejection, in the scientific community, because other guidelines continued to stress the need for a lifetime surveillance, given the evidence showing a lifetime risk of cancer. The present survey shows that the common belief is that there is a real risk of oversurveilling patients, and further studies are urgently needed to identify subsets of cysts suitable for follow-up discontinuation. Only 18% of responders would consider surveillance discontinuation after 5 years, as recommended by the AGA guidelines, but 54% believe there is not enough evidence to recommend lifetime follow-up because this practice is not associated with a decreased mortality for pancreatic cancer. Behind this conviction, there is a greater attention to issues such as health care resources, ethics, and the cost effectiveness of surveillance protocols, which have not yet been shown to decrease pancreatic cancer-related mortality, a fundamental prerequisite of any screening protocol. Further studies evaluating the most cost-effective surveillance protocols and identifying the most suitable population for surveillance discontinuation are mandatory.

Another controversial issue concerns the use of adjuvant therapy after surgery for invasive IPMNs. Available evidence is scarce,[21–24] often deriving from large national databases where fundamental data for the study of IPMNs is lacking, and recommendations are often derived from those for pancreatic ductal adenocarcinoma. Further studies, including randomized controlled trials, should identify populations that can benefit the most from adjuvant treatment.

The current study has several limitations. Most responders were European surgeons and gastroenterologists working in university or teaching hospitals. This factor limited the definition of the picture of PCNs management in smaller settings. However, it is easy to imagine how concerns identified in university or teaching hospitals might be exacerbated in smaller hospitals and among other specialties.

Conclusions

An analysis of PCN guidelines application in clinical practice demonstrated that 3 levels of discrepancies exist: among the 3 existing guidelines themselves, between guidelines and available evidence, and between guidelines and clinical practice. Primary low evidence areas are represented by the role of main pancreatic duct dilatation, mural nodules, cyst size and growth rate, cyst-related symptoms, and surveillance discontinuation. The update of the current guidelines, possibly attempting to merge them into a single universally accepted version, should focus on filling the gap of low evidence areas. For this purpose, an international consortium of experts named Verona Evidence-Based-Meeting gathered for the definition of future research lines with the aim of increasing the level of available evidence.

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