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REVIEW

Exploring the new Kyoto guidelines for managing pancreatic cysts: an overview and comparison with previous guidelines

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Abstract

The rising use of diagnostic imaging has led to an increase in the incidental detection of pancreatic cysts, with reported incidences of 1.2–2.6% on Computed Tomography and 2.4–49.1% on Magnetic Resonance Imaging. While many of these cysts are asymptomatic and benign, the enhanced imaging techniques have also revealed malignant and premalignant lesions. Mucinous neoplasms, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms, are particularly concerning due to their potential for malignant transformation. Recent studies highlight significant variations in dysplasia across IPMN types, with main duct IPMNs showing a higher likelihood of high-grade dysplasia or invasive carcinoma compared to branch duct IPMNs. Management and follow-up of these lesions remain controversial due to inconsistent guidelines. This article reviews and compares six major guidelines: the 2015 American Gastroenterological Association guidelines, the 2017 International Association of Pancreatology (IAP/Fukuoka) guidelines, the 2017 American College of Radiology guidelines, the 2018 American College of Gastroenterology guidelines, the 2018 European Study Group guidelines, and the newly released, 2024 Kyoto guidelines. We summarize key differences in risk factors, surveillance protocols, and surgical referral criteria, with a focus on the updated 2024 Kyoto guidelines and the implications of recent research advancements.

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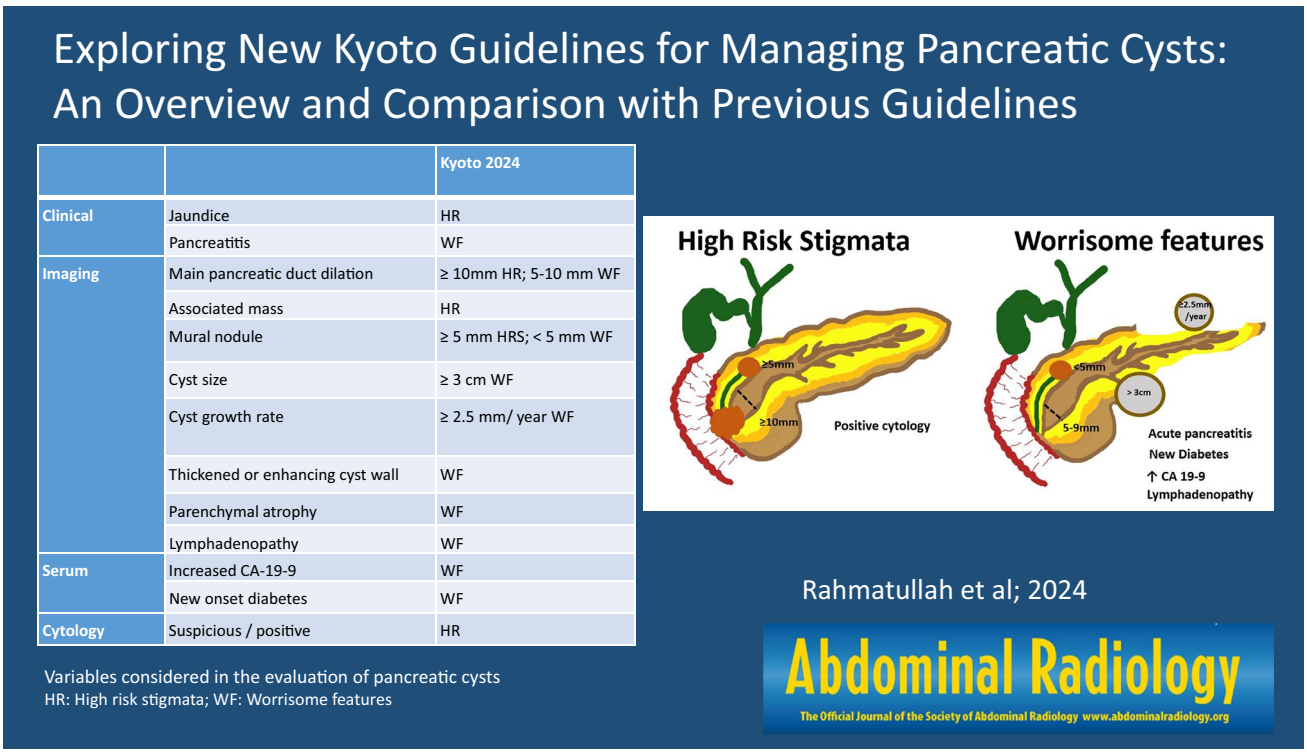
Graphical abstract



Keywords IPMN · Pancreatic cysts · Surveillance · Guidelines · International consensus · Kyoto guidelines

Introduction

As the utilization of diagnostic imaging continues to surge, there has been a corresponding increase in the detection of pancreatic cysts as incidental findings [1–3]. Studies indicate that the incidence of these cysts ranges between 1.2 and 2.6% on Computed Tomography (CT) and 2.4–49.1% on Magnetic Resonance Imaging (MRI) [4]. While many of these discovered cysts are asymptomatic and benign, the wider adoption of imaging techniques has also led to the identification of malignant and premalignant cysts. Furthermore, a single institute three-decade study showed that with the addition of better diagnostic tools, the agreement between preoperative and final histopathological diagnosis for pancreatic cysts increased by decade from 45%, to 68%, and in 2023 to 80% (up to 91% with the inclusion of molecular analysis) [5].

Among premalignant cysts, mucinous neoplasms constitute a significant concern as they possess the potential for malignant transformation. These include intraductal papillary mucinous neoplasms (IPMNs)—categorized into main duct (MD)-IPMNs, branched duct (BD)-IPMN, or mixed types—and mucinous cystic neoplasms (MCNs). A 2023 study in Finland reviewed 2,024 pancreatic resections, finding that 88 were due to IPMNs. Over half of these were MD-IPMNs, with the majority (61.7%) showing invasive carcinoma (IC). In BD-IPMNs, most (85.7%) had low-grade dysplasia (LGD), and in mixed-type IPMNs, about a third (33.3%) had IC [6]. A 2018 study investigating the annual cohort of patients undergoing a pancreatectomy in the American College of Surgeons National Surgical Quality Improvement Program found that in 478 pathologically-proven IPMN patients, 11 had high-grade dysplasia (HGD) and 97 had IC [7]. Additionally, studies have been done to compare MD-IPMNs and BD-IPMNs showing that patients with MD-IPMN had a higher likelihood of having HGD or IC [8, 9]. Given their increasing incidence, uncertain malignant potential, and an overall postoperative mortality of up to 2% and major morbidity of 30% [10], pancreatic cystic lesions pose significant concerns for both patients and healthcare providers. In addition, management and follow-up criteria for these patients are controversial due to varying guidelines.

This article compares six different guidelines currently being used: the 2015 American Gastroenterological Association (AGA) guidelines, the 2017 International Association of Pancreatology (IAP or Fukuoka) guidelines, the 2017 American College of Radiology (ACR)

guidelines, the 2018 American College of Gastroenterology (ACG) guidelines, the 2018 European Study Group guidelines, and the most recent revision of the Fukuoka, the 2024 Kyoto guidelines [4, 11–15] (Table 1). We aim to summarize and delineate key differences in the risk factors (Table 2), surveillance protocols (Table 3), and criteria for surgical referral (Table 4), with particular emphasis on the

Table 1 Comparison of the formulation of the guidelines

	AGA 2015	Fukuoka 2017	ACR 2017	ACG 2018	European 2018	Kyoto 2024
Cyst type	Asymptomatic pancreatic cystic neoplasms*	IPMNs	All pancreatic cysts	All pancreatic cysts**	All pancreatic cystic neoplasms	IPMNs
Methodology	Systematic review, GRADE methodology	Scientific review, expert consensus	Scientific review, expert consensus	Systematic review, GRADE methodology	Systematic review, GRADE methodology	Scientific review, expert consensus/evidence based

AGA American gastroenterological association, *ACR* American college of radiology, *ACG* American college of gastroenterology, *IPMN* intraductal papillary mucinous neoplasms

*Excluding solid papillary neoplasms, cystic degeneration of adenocarcinoma, neuroendocrine tumors, and main duct IPMN without branch duct involvement

**In patients without a strong family history of or predispositions to pancreatic cancer

Table 2 Variables considered in the evaluation of pancreatic cysts

		AGA 2015	Fukuoka 2017	ACR 2017*	ACG 2018	European 2018**	Kyoto 2024
Clinical	Jaundice		HR	HR	HR	AI	HR
	Pancreatitis		WF		HR	RI	WF
Imaging	Main pancreatic duct dilation	HR	≥10 mm HR; 5–9 mm WF	≥10 mm HR; ≥7 mm WF	>5 mm HR	≥10 mm AI; 5–9.9 mm RI	≥10 mm HR; 5–10 mm WF
	Associated mass	HR		Enhancing solid component is HR, non-enhancing mural nodule is WF	HR	AI	HR
	Mural nodule		≥5 mm HR; <5 mm WF		HR	≥5 mm AI < 5 mm RI	≥5 mm HR; <5 mm WF
	Cyst size	≥3 cm HR	≥3 cm WF	≥3 cm WF	≥3 cm HR	≥4 cm RI	≥3 cm WF
	Cyst growth rate		≥5 mm/2 years WF	Based on percentage increase	≥3 mm/year HR	≥5 mm/year RI	≥2.5 mm/year WF
	Thickened or enhancing cyst wall		WF	WF			WF
	Parenchymal atrophy		WF				WF
	Lymphadenopathy		WF				WF
Serum	Increased CA-19–9		WF		HR	RI	WF
	New onset diabetes				IRM	RI	WF
Cytology	Suspicious/positive				HR	AI	HR

AGA American gastroenterological association, *ACR* American college of radiology, *ACG* American college of gastroenterology, *AI* absolute indication for surgery, *RI* relative indication for surgery, *HR* high risk, *WF* worrisome features, *IRM* increased risk of malignancy

*ACR HR and WF are borrowed from the 2012 IAP guidelines [16] except for main pancreatic duct dilation with is based on a study by Kang et al. [17]

**Regarding IPMNs. The terms AI and RI for surgery are used instead of HR and WF

Table 3 Comparison of different guidelines' surveillance recommendations based on cyst size without any high risk, worrisome features, or progression in size

Size	AGA 2015	Fukuoka 2017	ACR 2017	ACG 2018	European 2018*	Kyoto 2024
< 1 cm	MRI in 1 yr, then every 2 for 5 yr	CT/MRI in 6 m, then every 2 yr	CT/MRI for cyst < 1.5 cm yearly if age < 65 q2 yr if age > 65, then lengthen For cysts with MPD communication 1.5–1.9 cm, CT/MRI q1 yr for 5 yr then lengthen, or EUS-FNA For cysts with MPD communication 2–2.5 cm, CT/MRI q6 m × 4 then lengthen, or, EUS-FNA For cysts without established MPD communication 1.5–2.5 cm: CT/MRI q6 m × 4 yr, then lengthen, or, EUS-FNA CT/MRI for cyst > 2.5 cm and low risk** q6 m for 4 yr, then lengthen If age > 80 and low risk**, image q2 yr	MRI q2 yr, lengthen after 4 yr	MRI and/or EUS with CA19-9 and clinical evaluation q6 m for 1 yr; if stable continue annually	MDCT/MRI after 6 m, then q18 m for 5 yr
1–2 cm		CT/MRI 6 m × 1 yr, yearly × 2 yr, then lengthen to 2 yr		MRI q1 yr for 3 yr, then MRI q2 yr for 4 yr, then lengthen		
2-3 cm		EUS in 3–6 m, then lengthen to 1 yr, alternating MRI with EUS		MRI/EUS q6–12 m for 3 yr, then MRI q1 yr for 4 yr, then lengthen		MDCT/MRI q6 m for 1 yr, then yearly
> 3 cm		Alternate MRI with EUS every 3–6 m		MRI alternating with EUS q6 m for 3 yr, then MRI alternating with EUS yearly for 4 years, then lengthen		MDCT/MRI q6 m
When to Stop Surveillance	After 5 yr if stable	Lifelong	After 10 years of stability	Lifelong	Lifelong	Consider after 5 yr vs lifelong

AGA American gastroenterological association, *ACR* American college of radiology, *ACG* American college of gastroenterology, *CT* computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, *q* every, *m* months, *yr* year

*Regarding IPMNs

** Low risk by imaging is defined as no mural nodules, no wall thickening, normal caliber MPD, no peripheral Ca++

Table 4 Comparison of guideline specific cyst features prompting surgical referral or resection

	Indications for Surgical Consultation
AGA 2015	Both a solid component and a dilated pancreatic duct Concerning features on EUS and FNA
Fukuoka 2017	Any HR features Any WF followed by an EUS with any of the following results: Definite mural nodule(s) ≥ 5 mm, main duct features suspicious for involvement, cytology suspicious or positive for malignancy Consider in young, fit patients with need for prolonged surveillance if size > 2 cm
ACR 2017	Any HR features Any interval growth (20% increase in long-axis diameter in axial or coronal)
ACG 2018	Any HR features A focal dilation of the pancreatic duct concerning for main duct IPMN or an obstructing lesion Presence of high-grade dysplasia or pancreatic cancer on cytology
European 2018*	1 or more AI Patient without significant co-morbidities and 1 or more RI Patient with significant co-morbidities and 2 or more RI
Kyoto 2024	Any HR if surgically appropriate Any WF and any of the following: repeated acute pancreatitis, multiple WF, young and fit for surgery

AGA American gastroenterological association, *ACR* American college of radiology, *ACG* American college of gastroenterology, *AI* absolute indication, *RI* relative indication, *HR* high risk, *WF* worrisome features, *EUS* endoscopic ultrasonography, *FNA* fine needle aspiration, *IPMN* intraductal papillary mucinous neoplasms

*Regarding IPMNs

newly revised 2024 Kyoto guidelines and advancements in research that should be explored.

2015 American gastroenterological association (AGA) guidelines

Method of formulation

Expert consensus systematic review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendation and associated quality of evidence is also provided for each suggestion.

Target population

All asymptomatic pancreatic cysts excluding solid pseudopapillary neoplasms, cystic degeneration of adenocarcinomas, cystic neuroendocrine tumors, and MD-IPMNs without side branch involvement.

Risk factors

Defines three risk factors as high risk (HR): the presence of an associated solid component, a cyst size ≥ 3 cm, and main pancreatic duct (MPD) dilation, with no specific cutoff value. The AGA guidelines describe the lowest number of risk factors compared to all other guidelines, with no mention of cyst growth rates, and state that more than two HR features are needed for further workup through endoscopic ultrasonography and fine needle aspiration (EUS-FNA).

Surveillance

The AGA guidelines recommend surveillance through a repeated MRI after one year and then every two years for five years if there is no change in size or characteristics. Note that the surveillance protocol is not dependent on cyst size unlike many other guidelines, and it has been shown that the risk of developing HR features is related to cyst size (16). The AGA guidelines suggest discontinuation of surveillance after five years if there is no change or concerning features. The guideline also mentions that surveillance may be inappropriate for patients who are not surgical candidates hence they should understand the risks and benefits of a cyst surveillance program.

Surgical indications

Surgical consultation is only considered if both a solid component and a dilated pancreatic duct are present, or if there are concerning features on EUS-FNA such as positive cytology.

Surveillance after resection

The AGA guidelines recommend that all patients with a resected cyst containing dysplasia or IC undergo MRI surveillance in the remaining pancreas every two years if the

patient is fit for surgery. However, if there is no surgery proven HGD or malignancy in pancreatic cysts, routine surveillance after resection is not advised according to the AGA guidelines.

2017 Fukuoka guidelines

Method of formulation

An expert consensus during the 2016 20th IAP meeting in Sendai, Japan. The recommendations do not include descriptions on the quality or strength of recommendations.

Target population

IPMNs.

Risk factors

The Fukuoka guidelines describe both HR and worrisome features (WF) of IPMNs. The HR features are described as "High Risk Stigmata" (HRS) and include obstructive jaundice, main pancreatic duct dilation ≥ 10 mm, or enhancing mural nodule(s) ≥ 5 mm. WF include a cyst size ≥ 3 cm, enhancing mural nodule < 5 mm, thickened enhanced cyst walls, MPD size of 5-9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, lymphadenopathy, an elevated serum level of CA19-9 and a cyst growth rate ≥ 5 mm/2 years.

Surveillance

MRI with magnetic resonance cholangiopancreatography (MRCP) or a pancreatic protocol CT are the preferred surveillance methods. Surveillance is based on cyst sizes in the Fukuoka guidelines, with an initial six-month follow-up for all sizes, and larger cyst sizes requiring more frequent imaging. After the initial follow-up, a cyst < 1 cm requires the next follow-up after 2 years, 1–2 cm after a year, and > 2 cm after 6 months. Indications for EUS include the presence of any WF or alternating with MRI in regularly scheduled follow-ups for cysts > 2 cm (every year) and > 3 cm (every three to six-months). The Fukuoka guidelines advise lifelong surveillance, or until the patient is no longer a surgical candidate.

Surgical indications

The presence of any HR findings, or WF followed by an EUS with either a definite mural nodule(s) ≥ 5 mm, main duct features suspicious for involvement (the presence of any one of thickened walls, intraductal mucin or mural nodules), or suspicious/positive cytology, warrant a surgical referral given the patient is surgically fit. Also, for BD-IPMNs, these guidelines mention that surgery can be considered in young, fit patients with the need for prolonged surveillance if the cyst size is > 2 cm, and should be strongly considered in young, fit patients if the size is > 3 cm.

Surveillance after resection

The Fukuoka guidelines recommend continuing surveillance after resection every 6–12 months, with imaging being recommended twice a year if there is a family history of pancreatic ductal adenocarcinoma (PDAC), a surgical margin positive for HGD, or non-intestinal subtype of resected IPMN. Surveillance is to be continued if the patient is fit to undergo another surgery.

2017 American college of radiology (ACR) guidelines

Method of formulation

A review of published literature with recommendations made by expert consensus (four radiologists, a gastroenterologist, and a pancreatic surgeon). The recommendations do not include descriptions on the quality or strength of recommendations.

Target population

Incidentally identified asymptomatic pancreatic cysts.

Risk factors

The summarized HR and WF in the ACR guidelines are from the 2012 IAP multi-authored consensus guidelines (17). The HR features are described as "High Risk Stigmata" and include obstructive jaundice with a cyst in the head of the pancreas, an enhancing solid component within the cyst, and a MPD dilation ≥ 10 mm. WF include a cyst size ≥ 3 cm, thickened or enhancing cyst wall, non-enhancing mural nodule, and MPD diameter ≥ 7 mm. The MPD diameter used as a WF is based on a study by Kang et al. [17].

Surveillance

The ACR guidelines recommend surveillance through MRI or pancreatic protocol CT, noting the excellent ability of MRCP to assess ductal communication. Similar to other guidelines, the ACR takes cyst size into account for scheduled screening, but unlike other protocols, the cyst size cut offs are different, such as < 1.5 cm, 1.5–2.5 cm,

and > 2.5 cm. Also, the ACR guidelines integrate patient age recommendations for surveillance schedules. Particularly, patients over 80 years are advised to undergo less frequent screening compared to those under 65. It also has different surveillance schedules based on established communication with the MPD. For cysts < 2.5 cm, any HR, WF or interval growth warrant an EUS-FNA while for cysts ≥ 2.5 cm, HR, WF or interval growth warrant both an EUS-FNA and a surgical consultation. The ACR goes into the most detail about the specifics of cyst growth rates as it can help differentiate malignant cysts and recommends radiologists to report the cyst growth when possible. For cysts < 0.5 cm, growth is represented by a 100% increase, for cysts 0.5–1.5 cm, a 50% increase, and for cysts > 1.5 cm, a 20% increase in the long-axis diameter. The ACR suggests discontinuation of surveillance after 10 years of stability, or sooner if stability is achieved and the patient reaches 80 years of age, or the patient is no longer surgically fit.

Surgical indications

These include the presence of any HR findings and any significant interval growth as factors that point to resection. Furthermore, according to the ACR guidelines, the appearance of any mural nodule, wall thickening, dilation of MPD ≥ 7 mm and jaundice during surveillance highlights the need for urgent EUS-FNA and surgical referral regardless of cyst size and growth.

Surveillance after resection

The ACR guidelines do not mention follow-up surveillance of the pancreas once a cyst has been removed.

2018 American college of gastroenterology (ACG) guidelines

Method of formulation

A systematic review of the literature and expert consensus recommendations by gastroenterologists. The GRADE methodology was used to determine the strength and quality of the evidence used to formulate the guidelines.

Target population

Pancreatic cysts in patients without a strong family history of pancreatic cancer or known genetic predispositions to pancreatic cancer.

Risk factors

The ACG guidelines only detail HR features instead of both WF and HR as done in other guidelines. These include jaundice, acute pancreatitis, increased serum CA 19–9, mural nodules or solid components, MPD diameter of > 5 mm or change in main duct caliber with upstream atrophy, cyst size ≥ 3 cm, increase in cyst size ≥ 3 mm/year, and cytology with HGD/IC. According to the ACG guidelines, new onset or worsening diabetes mellitus also suggest an increased risk of malignancy. It is of note that compared to other guidelines, the MPD is considered HR at a lower value and the ACG guidelines have a more aggressive take on the growth rate with ≥ 3 mm/year as HR.

Surveillance

The ACG guidelines recommend surveillance through MRI or MRCP but mention pancreatic protocol CT and EUS as excellent alternatives. They also stratify the surveillance schedules based on cyst sizes, with larger cysts requiring more frequent imaging. A cyst < 1 cm requires the next follow-up after 2 years, 1–2 cm after a year, and > 3 cm after 6 months. If the patient is a surgical candidate, lifelong surveillance is recommended, except for patients aged 76–85 years as an individualized surveillance plan is deemed appropriate for this age group. They mention that patients who are not candidates for surgery should not undergo further evaluation of incidentally found pancreatic cysts, irrespective of cyst size. The guidelines also mention that if serous cystadenomas or pseudocysts are diagnosed, surveillance can be stopped. EUS-FNA is indicated in cases where the cysts size ≥ 3 cm, MPD diameter > 5 mm or a change in main duct caliber with upstream atrophy, presence of mural nodule or solid component, growth rate ≥ 3 mm/year, suspected IPMN or MCN ≥ 3 cm, or jaundice or pancreatitis attributed to the cyst.

Surgical indications

Surgical referral is indicated when there are any HR features, a focal dilation of the pancreatic duct concerning for MD-IPMN or an obstructing lesion, or the presence of HGD/IC on cytology. Solid-pseudopapillary neoplasms are also to be referred for surgery.

Surveillance after resection

The ACG guidelines specify that resected benign cysts and MCNs without IC do not require postoperative surveillance. However, for patients with a resected solid-pseudopapillary neoplasm, yearly surveillance for a total of five years is recommended. The ACG guidelines also specify that all

resected IPMNs require lifelong surveillance with HGD requiring surveillance with MRI/EUS every six months, and patients with LGD, in the absence of pancreatic cysts in the remnant, need MRI surveillance every two years.

2018 European study group guidelines

Method of formulation

A multidisciplinary panel of multiple European countries used systematic reviews and the GRADE methodology to assess the strength of each recommendation.

Target population

All pancreatic cysts.

Risk factors

The European guidelines use the terms "Absolute Indications (AI)" and "Relative Indications (RI)" for surgery instead of "HR" and "WF", respectively, when a patient presents with an IPMN. AI include jaundice, an enhancing mural nodule (≥ 5 mm) or a solid component, positive cytology, or a MPD measuring ≥ 10 mm. RI include pancreatitis, new onset diabetes, MPD dilatation 5–9.9 mm, cyst growth rate ≥ 5 mm/year, increased level of serum CA 19–9, enhancing mural nodules (< 5 mm), and a cyst diameter ≥ 40 mm. Notably, CA 19–9 levels are both a RI and a mode of surveillance in the European guidelines.

Surveillance

The European guidelines are the most specific about managing different types of pancreatic cystic neoplasms. Note that their MRI surveillance protocol does not depend on cyst size. It has been shown that the risk of developing HR and WF are related to cyst size [18].

(1) IPMN: a six-month follow-up for the first year with a clinical evaluation, serum CA 19–9, and MRI and/or EUS, then lifelong annual surveillance, regardless of cyst size, if the patient remains surgically fit; (2) MCN: A lesion < 40 mm, in the absence of risk factors or symptoms, should undergo surveillance every six months for the first year, and then lifelong annual surveillance if the patients remains a surgical candidate; (3) Serous cystic neoplasm (SCN): Asymptomatic patients should be followed for one year. After one year, follow-up is recommended only in symptomatic patients; (4) Other cysts: Cysts of unclear etiology measuring < 15 mm with no risk factors for malignancy should be re-examined after one year. If the cyst is stable for three years, follow-up may be extended to every two years. Cysts ≥ 15 mm should receive follow-up annually after the first year with both MRI and EUS-FNA. This would be lifelong unless the patient is unwilling or unfit for surgery as no follow-up is required if a patient is not a surgical candidate.

Surgical indications

(1) IPMN: Indications for surgery include one or more AI, or one/two RI considering the patient's comorbidities; (2) MCN: Indications for surgical referral include size ≥ 4 cm, mural nodule, solid mass, positive cytology, or associated symptoms; (3) SCN: Surgery is recommended only in patients with symptoms related to mass effect on adjacent organs; (4) Other cysts: solid pseudopapillary neoplasms should be resected and cystic neuroendocrine tumors should be resected if they are ≥ 2 cm or symptomatic.

Surveillance after resection

The European guidelines recommend lifelong surveillance of an IPMN with HGD or a MD-IPMN, needing a follow-up every six months for the first two years after resection followed by yearly surveillance. Furthermore, IPMNs with LGD or the presence of an IPMN in the remnant pancreas should follow the same surveillance protocols as non-resected IPMNs. Post resections surveillance for SCN is not recommended and is not specified for other types of cysts.

2024 Kyoto guidelines

Method of formulation

An expert consensus during the 2022 26th meeting of the IAP in Kyoto, Japan, aimed to revise the 2017 Fukuoka guidelines. All the recommendations in the revised Kyoto guidelines have been graded based on evidence levels.

Target population

IPMNs.

Risk factors

HR features are described as "High Risk Stigmata" and include obstructive jaundice, an enhancing mural nodule ≥ 5 mm or a solid component, MPD ≥ 10 mm, and new additions include, an associated mass and positive/suspicious cytology being added as HR (Fig. 1). WF include acute pancreatitis, increased CA19-9 levels, cyst size ≥ 30 mm, an enhancing mural nodule < 5 mm, thickened or enhancing cyst walls, MPD 5 mm and < 10 mm, an abrupt change in caliber of pancreatic duct with

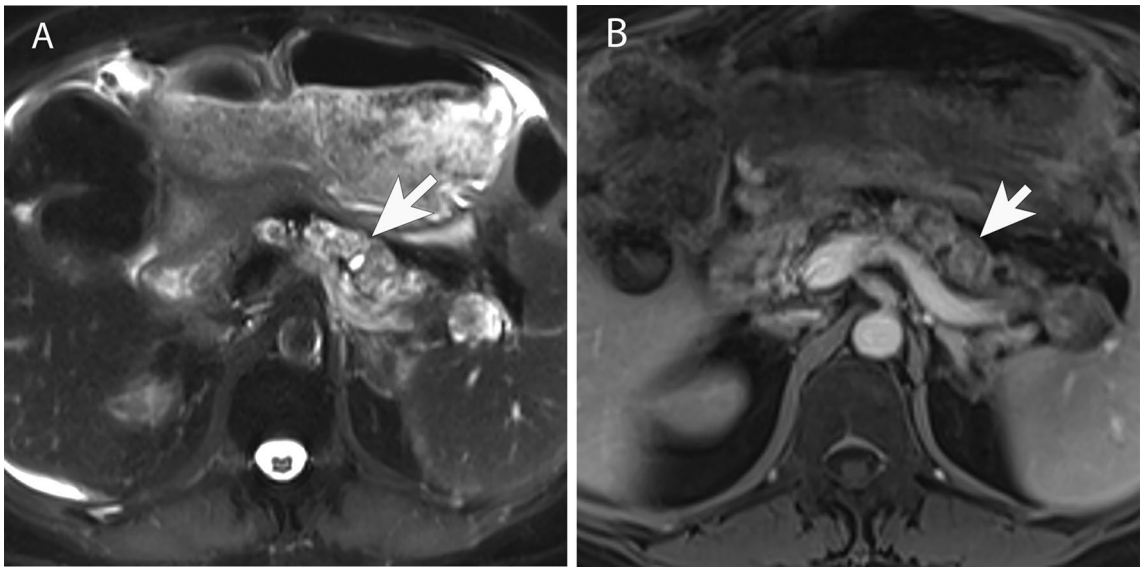


Fig. 1 53-year-old woman with moderately differentiated pancreatic ductal adenocarcinoma in the setting of main duct IPMN. **A** Axial T2 weighted images a dilated main pancreatic duct to up to 17 mm containing nodules of intermediate signal (arrow). **B** Axial post contrast T1 weighted image shows enhancement of these nodules. EUS guided FNA confirmed the diagnosis of moderately differentiated pancreatic ductal adenocarcinoma arising in the background of main duct IPMN

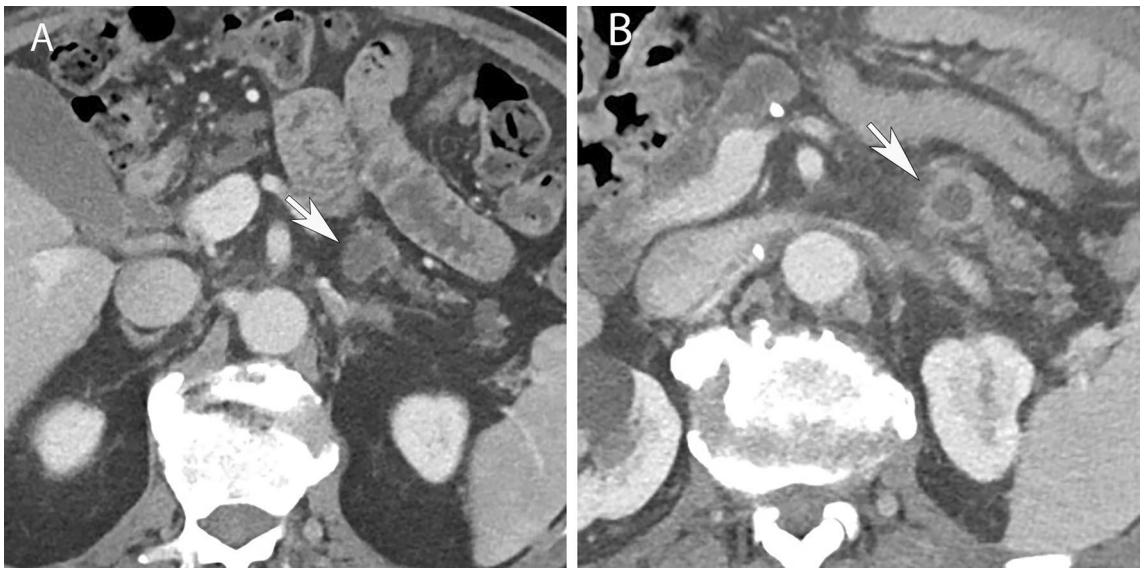


Fig. 2 77-year-old man with history of moderate to poorly differentiated pancreatic ductal adenocarcinoma post Whipple in the background of IPMN undergoing surveillance of pancreatic tail cyst. **A** Axial venous phase CT shows a 15 mm cyst with thin walls, likely a side branch IPMN (arrow). **B** Axial venous phase CT obtained 3 years later demonstrated interval development of wall thickening (arrow) of the same cyst (considered a worrisome feature in the Kyoto guidelines). EUS guided FNA of this lesion showed poorly differentiated pancreatic ductal adenocarcinoma in the setting of a side branch IPMN

distal pancreatic atrophy, and lymphadenopathy (Fig. 2). Changes in the WF include the addition of new onset or acute exacerbation of diabetes mellitus and the cyst growth rate of ≥ 2.5 mm/year (previously ≥ 5 mm/2 years). Overall, the Kyoto guidelines are the most descriptive in the evaluation of HR and WF (Fig. 3).

Surveillance

Surveillance imaging is recommended by contrast-enhanced multi-detector CT (MDCT) or MRI/MRCP, including EUS/contrast-enhanced EUS (CE-EUS) too. For all cysts an initial six-month follow-up is required and for cysts < 2 cm,

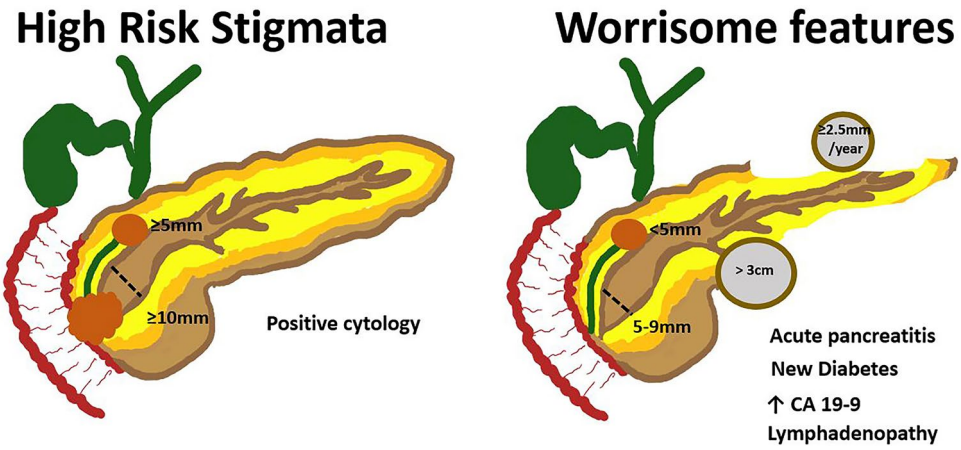


Fig. 3 Diagrammatic representation of High Risk Stigmata (HRS) and Worrisome features of the Kyoto guidelines. The HRS are (1) obstructive jaundice secondary to pancreatic head mass, (2) enhancing mural nodule ≥ 5 mm or a solid component, (3) main pancreatic duct ≥ 10 mm, and (4) suspicious or positive cytology results (if performed). WF are (1) acute pancreatitis, (2) increased serum level of CA19-9, (3) new onset or acute exacerbation of diabetes mellitus (DM) within the past year, (4) cyst ≥ 30 mm, (5) enhancing mural nodule < 5 mm, (6) thickened/enhancing cyst walls, (7) main pancreatic duct (MPD) ≥ 5 mm and < 10 mm, (8) abrupt change in the caliber of the pancreatic duct with distal pancreatic atrophy, (9) lymphadenopathy, and (10) cystic growth rate ≥ 2.5 mm/year [6]. These factors are mostly unchanged from the previous version, except for new onset or recent exacerbation of DM and the cyst growth rate

the guidelines recommend MDCT/MRI every eighteen months for five years. For cysts 2–3 cm, imaging is to be done every six months for the first year, then yearly while for cysts > 3 cm, it is to be done every six months. The Kyoto guidelines also differ from the Fukuoka guidelines as it gives two options, "stop surveillance" or "continue surveillance", for small unchanged BD-IPMN after 5 years surveillance, as there is a need of more evidence to come to definite conclusion regarding ending surveillance. The candidates to stop surveillance in are those with stable small cysts (< 2 cm) without WF or HR features, and cysts that remain unchanged for a period of 5 years. Surveillance can also be stopped in patients who are unfit for surgery or have a life expectancy of less than ten years. Furthermore, deciding to continue or end surveillance, especially in older patients, should be determined based on patients' general condition, comorbidity, life expectancy, and preference. MRI with physical examination, assessment of tumor marker and new onset diabetes are the preferred ways to provide surveillance, and MDCT and EUS should be considered when changes are observed in the MRI.

Surgical indications

Surgical indications include any HR features and the presence of multiple WF as the more WF are present, the likelihood of HGD increases. The Kyoto guidelines consider if the patient is young and a surgical candidate, as well as the presence of repeated episodes of pancreatitis as an indication since they affect the patient's quality of life.

Surveillance after resection

The Kyoto guidelines protocols are similar to the Fukuoka, with yearly continuous imaging and patients only needing imaging twice a year if there is HGD or a family history of pancreatic cancer. Additionally, in patients who undergo total pancreatectomy for a non-invasive lesion, IPMN-specific surveillance can be stopped if there have been no concerning findings during a 5 year postoperative surveillance period.

Performance of the previous and new additions in the 2024 Kyoto guidelines

Due to the various guidelines worldwide and the multidisciplinary care required in the case of pancreatic cysts, the performance of each guideline becomes invaluable. It has been previously reported that nearly 7 out of 10 radiologists call for a global consensus on the management of incidental pancreatic cystic lesions. The anonymous survey mostly received responses from radiologists (306 of 323; 94.7%) in North America and found that the ACR recommendations are widely adopted (42.5%), with homegrown systems (15.0%) and the Fukuoka guidelines (7.8%) being the next most utilized approaches [19]. Adherence to surveillance protocols is another concern. Single center studies have reported a loss to follow-up imaging ranging from 28 to 53%, with an additional decline in follow-up over time and unsatisfactory adherence to guidelines [20, 21]. A reason for this could be certain guidelines

recommending lifelong follow-up, which can prove to be costly and a burden on the healthcare system. A study compared the Fukuoka and AGA guidelines, finding that while deaths linked to pancreatic cyst management and quality-adjusted life years were comparable, the Fukuoka guidelines had fewer instances of missed cancers due to the more intensive surveillance approach, which was counterbalanced by higher expenses ($168.3 vs $89.4 million). This consideration gains significance given the global adaptation of guidelines [22]. These sentiments were echoed in a separate study, which concluded that utilizing the Fukuoka guidelines for managing pancreatic cystic lesions might not be cost-effective and could potentially elevate mortality rates due to overtreatment of low-grade cysts. The incremental cost-effectiveness ratio for monitoring pancreatic cysts was $171,143 per quality-adjusted life year (QALY) when compared to no surveillance or surgery. This ratio could decrease to $80,707 per QALY if overtreatment of low-grade cysts is avoided. It was suggested that the specificity for risk stratification of high-risk cysts must surpass 67% to justify the cost-effectiveness of surveillance [23].

Multiple studies have been done to evaluate the performance of these guidelines (Table 5). It was shown that many of these guidelines have been proven to be similar in gauging the initial risk. There is evidence suggesting that the use of WF and HR features in guidelines for pancreatic cysts, such as the Fukuoka guidelines, can contribute to false positives, leading to unnecessary interventions. WF, including features like large cyst size or thickened walls, and HR features, such as a solid component or duct dilation, are often seen in benign cysts. This results in many benign lesions being incorrectly flagged as malignant, leading to overtreatment [24]. A 2019 review further compared studies and noted that adherence to the Fukuoka guidelines is likely to result in more benign resections but fewer instances of missed cancers. However, it did emphasize that a direct comparison is challenging due to differences in methodology, criteria, and discrepancies in outcome measures [25]. A 2019 meta-analysis agreed that while the AGA and Fukuoka guidelines were comparable, the diagnostic accuracy is still "unsatisfactory" based on the low pooled sensitivity (0.59 and 0.67, respectively) and specificity (0.77 and 0.64, respectively). Hence, they suggested these guidelines should only be used as a broad framework [26]. The inclusion of "if surgically appropriate" in Kyoto 2024 provides a crucial layer of consideration for those patients who may not be candidates for treatment. However, monitoring patients who are not suitable for surgery can lead to unnecessary psychological distress and resource strain. In cases where intervention is not possible, it makes little sense to continue frequent monitoring, as it may not change the course of the disease or improve outcomes.

These conflicting studies have underscored the necessity for further refinement of existing guidelines, thus prompting a warm reception for the Kyoto 2024 guidelines. Although investigations regarding the efficacy of this guideline are pending, it has revised the criteria of HR and WF, aimed to streamline the surveillance protocols for non-resected IPMNs, and given the option to both continue and discontinue surveillance based on risk factors. It has also detailed pathological aspects and cyst fluid biomarkers that new research has shown to be beneficial in differentiating cyst types and distinguishing IPMN/MCN with LGD from HGD/IC. However, the need for more data on these topics is highlighted. Furthermore, given the distinct differences in morbidity and mortality between pancreaticoduodenectomy and distal pancreatectomy, there is a valid argument for having separate guidelines based on the location of the tumor. Pancreaticoduodenectomy, due to its complexity and involvement of multiple organs, carry higher risks and longer recovery times compared to distal pancreatectomy, which is associated with fewer complications. Tailoring guidelines for pancreatic head versus body/tail tumors could help optimize patient care by accounting for these variations in surgical outcomes [27, 28].

Future directions

The Kyoto guidelines have touched on the recent developments on cyst fluid analysis and the mutations that can help discriminate mucinous cysts. Analyzing mutations for TP53, SMAD4, CDKN2A, and PIK3CA may be helpful in identifying the presence of HGD/IC, with low sensitivity (9–39%) but high specificity (92–98%). It touches on studies using serum microRNA or circulating cell-free DNA with two reports assessing cell-free DNA of IPMN patients and detecting GNAS mutation in 32% and 72%, while KRAS mutation in 6% and 0% of IPMN patients [4, 34, 35]. It also notes that VHL mutations with neither KRAS nor GNAS is associated with > 99% sensitivity for a serous cystic neoplasm [4]. As reported previously, these recent discoveries underscore the possibility of inadvertently causing more harm than benefit by subjecting a large population to costly, lifelong imaging and unnecessary surgery. These tests, while valuable, represent only a fraction of a broader diagnostic approach that includes clinical assessment, blood testing, and the detection of mutations through cyst fluid sequencing. Such comprehensive methods may unveil up to 80% of IPMNs, with the potential to identify high-grade dysplasia or cancer, thereby potentially obviating the necessity for surveillance of low-risk lesions [36, 37].

Due to the variability of EUS and EUS-FNA results, a novel imaging technique, a needle-based confocal laser endomicroscopy (nCLE) has been introduced as a potential

Table 5 Comparison of the performance of the guidelines

Studies	Guidelines Used	Outcome	Result	Performance/Conclusion
2023 Van Huijgevoort et al. [29]	AGA 2015, Fukuoka 2017, European 2018	Detect HGD/IC in IPMNs	In HGD/IC, the AGA, Fukuoka, and European correctly advised surgery in 27%, 94% and 96%, respectively Without HGD/IC, the AGA, Fukuoka, and European incorrectly advised surgery in 8.6%, 83%, and 76%	The European and Fukuoka guidelines are superior in detecting HGD/IC in IPMNs compared to the AGA, but at the cost of a higher rate of unnecessary surgery
2021 Bulcke et al. [30]	AGA 2015, Fukuoka 2017, European 2018	Accuracy of detecting malignant cysts	Fukuoka, European and AGA had a sensitivity of 66.8%, 95.5%, 80%; a specificity of 26.8%, 11.3%, 43.8%; a PPV of 31.8%, 35%, 47.1% and a NPV of 61.1%, 83.3%, 77.8% respectively The missed malignancy rate was respectively 11.3%, 1.5%, 7.7% and surgical overtreatment was respectively 48.4%, 59.1%, 34.6%	The European guideline exhibited the lowest number of overlooked malignancies, but with a significant increase in the number of unnecessary surgeries. The Fukuoka guideline had the highest missed malignancies. The AGA guideline demonstrated the lowest number of unnecessary surgeries, but with a notable increase in missed malignancies
2020 Kovacevic et al. [31]	Fukuoka 2017, European 2018	Compare diagnostic performance	No difference in the performance of the guidelines with AUC values ranging from 0.572–0.610 and 0.607–0.621 for the Fukuoka and European guidelines respectively	The guidelines performed equally but the European guidelines had a slightly higher mean specificity
2020 Sun et al. [32]	European 2018, ACG 2018	Predicting advanced pancreatic cystic lesions	For the criteria having at least two indications, ACG was superior to European AI ($P=0.001$) but comparable to European RI ($P=0.12$) $EEG^{AM} \geq 1$ indication criteria were superior to ≥ 2 indications criteria ($P=0.02$). $EEG^{RM} \geq 1$ indication criteria had comparable diagnostic performance with ≥ 2 indications criteria ($P=0.86$) ACG ≥ 2 indications criteria were superior to ≥ 1 indication criteria ($P=0.02$)	Both guidelines were found to be helpful with comparable performance

Table 5 (continued)

Studies	Guidelines Used	Outcome	Result	Performance/Conclusion
2020 Park et al. [33]	Sendai 2016, Fukuoka 2012, Fukuoka 2017, European 2018	Likelihood of malignancy defined as high grade dysplasia and invasive carcinoma	PPV of HR features for Sendai, Fukuoka 2012, Fukuoka 2017 and AI European 2018 were 53%, 76%, 78% and 78% respectively. NPV of the Sendai, Fukuoka 2012 and Fukuoka 2017 were 100%, while that of the European 2018 was 92%. Risk of malignancy for patients with ≥ 4 WF (Fukuoka 2017) and ≥ 3 RI (European 2018) was 66.7% and 75.0% respectively	Each of the four guidelines were beneficial during the initial malignancy risk stratification. The Fukuoka 2017 guideline demonstrated the highest PPV and NPV

AGA American gastroenterological association, *ACR* American college of radiology, *ACG* American college of gastroenterology, *HGD/IC* high-grade dysplasia/invasive carcinoma, *IPMN* intraductal papillary mucinous neoplasms, *AI* absolute indication, *RI* relative indication, *HR* high risk, *WF* worrisome features, **EEGAM* European absolute + MCN, *EEGRM* European relative + MCN

way to better differentiate pancreatic cysts as it enables real-time in vivo microscopic imaging during EUS-FNA [38]. Specific imaging patterns are found with certain pancreatic cystic lesions such as fern like appearance found in SCNs and fingerlike papillary projections found in IPMNs. A 2022 systematic review and meta-analysis used 7 studies to evaluate the ability to differentiate mucinous and non-mucinous lesions. It reported a pooled sensitivity, specificity, and accuracy of 85%, 99% and 99%, respectively, with very low adverse effects [39]. Another study evaluated EUS-guided nCLE's ability to differentiate IPMNs with HGD/IC from those with LGD. It found that quantification of papillary epithelial width and darkness identified HGD/IC in IPMNs with high accuracy, and hence can be used in multicenter studies for risk stratification of IPMNs [40]. EUS-guided through-the-needle micro-biopsy using microforceps biopsy (MFB) devices allow cyst wall sampling and is another tool to improve the diagnostic accuracy of biopsies of pancreatic cysts by allowing larger tissue biopsy. A 2021 meta-analysis including a total of 463 patients found technical success in 98.5%, with a tissue acquisition yield of 88.2% and diagnostic accuracy of 68.6%. However, it was noted that these procedures were conducted by experts and adverse events occurred in 9.7%, highlighting that further studies are needed to evaluate the safety profile of using MFB devices [41]. The Kyoto guidelines also mention CE-EUS as a surveillance method. CE-EUS is a non-invasive endoscopic technique utilizing microbubble contrast media injected intravenously. Harmonic imaging settings allow for the contrast enhancement to visualize the parenchyma and small vessels, which would aid in distinguishing necrotic debris as seen in pseudocysts from enhancing mural nodules seen as a WF or HRS in IPMNs or MCNs. This can be performed by either color Doppler or contrast harmonic mode. A 2021 systematic review and meta-analysis including 532 patients found a pooled diagnostic accuracy of 89.6% in identifying mural nodules. The use of contrast-harmonic mode improved diagnostic accuracy to 95.6%. A positive contrast harmonic EUS increased the disease probability to 88% and a negative test reduced the probability to 2% [42]. Radiologists without access to advanced tools like nCLE should rely on imaging techniques such as CT, MRI, and EUS to evaluate pancreatic cysts, focusing on WF or HRS. It's important to consider whether a patient is a surgical candidate to avoid overtreatment, and multidisciplinary collaboration is essential for effective management.

The use of artificial intelligence, risk prediction models, and radiomics has been a rapidly developing research field that has shown significant benefit in evaluating pancreatic cysts and predicting malignancy using logistic regression and machine learning [43, 44]. A radiomics study proposed a computer-aided diagnosis (CAD) model that would help IPMN risk classification from MRI. Through evaluation

using multi-center datasets consisting of 246 MRI scans from five centers, they attained an unprecedented accuracy of 81.9% with the inclusion of radiomics, which outperforms the deep learning models without the utilization of radiomics [45]. Another study used a CT radiomics model which also performed better than the 2017 Fukuoka in classifying malignant IPMNs [46]. Additionally, integrating radiomics with imaging findings or clinical parameters notably enhanced the accuracy in distinguishing between cyst types compared to relying solely on radiomics ($P < 0.05$) [47, 48].

Nikiforova et al. developed and validated a 74-gene DNA/RNA-targeted NGS panel, known as PancreaSeq Genomic Classifier. They reported a 95% sensitivity and 100% specificity for a cystic precursor neoplasm, and the sensitivity and specificity for advanced neoplasia were 82% and 100%, respectively. In comparison, associated symptoms, cyst size, duct dilatation, mural nodule, enlarging cyst, and positive cytopathology had lower sensitivities (41–59%) and specificities (56–96%) for advanced neoplasia. In addition, this test increased the sensitivity of the AGA and Fukuoka guidelines while maintaining their inherent specificity [49]. Furthermore, a cyst classifier test, known as CompCyst, employed a supervised machine learning system utilizing clinical features, imaging traits, and genetic and biochemical markers. Comparative analysis revealed that CompCyst outperformed traditional clinical methods in categorizing pancreatic cystic lesions into surgical, surveillance, or non-surveillance groups. Moreover, the application of CompCyst spared surgery for over half of the patients who underwent unnecessary procedures [50]. While more studies need to be performed validating the reproducibility of these models and accounting for the global availability of these techniques, they accentuate the exciting developments that could potentially streamline the management of pancreatic cysts.

Conclusion

This review highlights both the overlap and contrast between the multiple guidelines available regarding management of pancreatic cysts. Although differences in guidelines can contribute to the challenges of management planning, it is essential to recognize the numerous fundamental similarities across guidelines. Though the guidelines consolidate existing evidence and factor in expert opinion, there are no prospective comparative trials that assess the performance of the various guidelines or on the performance of the newly established Kyoto guidelines. While the Kyoto guidelines have included new developments in research such as cyst fluid genetic analysis, there is a pressing need to further explore topics such as artificial intelligence, machine learning tools, gene classification systems, as well as new diagnostic tools such as nCLE on a large scale. These could help unveil the best surveillance criteria, especially for low-risk cysts, and significantly decrease the financial and psychosocial strain of lifelong surveillance on the patient and healthcare systems.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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