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Portuguese Pancreatic Club Perspective on the Surveillance Strategy for Intraductal Papillary Mucinous Neoplasms: When and How to Do It?

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Keywords
Intraductal papillary mucinous neoplasm · Pancreatic cancer · Surveillance

Abstract

Background: Pancreatic cysts are increasingly recognized nowadays, with estimated prevalence that may reach 50% in aging populations. Most cysts are of benign origin, and only a small proportion has malignant potential, including intraductal papillary mucinous neoplasms (IPMNs). Since pancreatic cysts are common, the most important goal was to identify the small percentage at high risk of developing malignancy. The increased detection and awareness of IPMNs led to the development of several consensus and guidelines, with only the most recent being evidence-based. ***Summary:*** Current consensus guidelines recommend risk assessment to prioritize high-risk patients for malignancy. In the Fukuoka/Kyoto guidelines, the predictive factors of malignancy are called "high-risk stigmata" and "worrisome features." Conversely, other guidelines consider the terms "absolute indication" and "relative indication" for surgery, as well as criteria for referral to multidisciplinary groups. In case of non-resected IPMNs, criteria for surveillance depend on cyst size, with magnetic resonance imaging pointed as the most consensual modality for follow-up, although the recommended imaging modality varies among consensus. In some situations, namely, older age, frailty/comorbidities, or stability of cyst size, follow-up discontinuation may be considered. ***Key Message:*** Performance of surveillance guidelines is measured by the ability to identify patients with high-grade dysplasia/early stage-invasive cancer. Guidelines with more intense protocols will likely lead to fewer missed cancers, balanced by a greater number of benign resections. Multidisciplinary management preferably in reference centers is of utmost importance given the indolent and complex

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nature of the disease, and a global evidence-based guideline that combines the several guidelines' groups is mandatory to uniformize care. In this review, the Portuguese Pancreatic Club summarizes the risk assessment and surveillance strategy of a patient with an IPMN according to different guidelines in order to create an updated perspective and to guide clinical care.

Perspetiva do Clube Português do Pâncreas sobre a Vigilância das Neoplasias Papilares Intraductais do Pâncreas: Quando e Como Vigiar?

Palavras Chave
Neoplasia mucinosa papilar intraductal do pâncreas · Neoplasia do pâncreas · Vigilância

Resumo
Contexto: Os quistos do pâncreas constituem uma entidade com incidência crescente, com uma prevalência que pode atingir os 50% em indivíduos idosos assintomáticos. A maioria dos quistos são benignos, com apenas uma pequena percentagem a apresentar risco de malignização, incluindo as neoplasias papilares intraductais do pâncreas (IPMNs). Uma vez que os quistos do pâncreas são comuns, importa identificar a pequena percentagem com risco de malignidade. O aumento da deteção desta entidade levou à publicação de inúmeras recomendações/consensos, em que apenas as mais recentes são baseadas na evidência. ***Sumário:*** A evidência atual recomenda a avaliação do risco de todos os doentes com IPMNs de forma a priorizar aqueles de alto-risco para malignidade. As recomendações de Fukuoka/Kyoto identificam fatores preditores de neoplasia como "estigmas de alto risco" e "características/sinais de alarme." Outros consensos utilizam os termos "indicação absoluta/relativa para cirurgia," assim como critérios de referenciação para equipas multidisciplinares. Nos doentes com IPMNs não ressecadas, a estratégia de vigilância depende do tamanho do quisto, sendo a ressonância magnética o método de imagem mais consensual, embora possa diferir entre consensos. Em alguns casos, nomeadamente por idade avançada, fragilidade/comorbilidades ou estabilidade do tamanho do quisto, pode ser considerada a descontinuação da vigilância. ***Mensagens-chave:*** A acuidade das guidelines de vigilância é medida pela capacidade de identificar doentes com displasia de alto grau/cancro invasivo em fase precoce. Guidelines com protocolos mais intensivos levarão a menos casos de cancro não detetados, à custa de um maior número de ressecções benignas. A avaliação multidisciplinar, preferencialmente em centros de referência, é essencial dada a natureza indolente e complexa desta doença. A elaboração de um consenso internacional unificado que junte os vários grupos de peritos revela-se essencial para uniformizar os cuidados de saúde. Nesta revisão, o Clube Português do Pâncreas pretende sumarizar a avaliação de risco e estratégia de seguimento de IPMNs conjugando as diferentes perspetivas/recomendações já publicadas e fornecendo mais uma ferramenta de abordagem nestes doentes.

Introduction

Pancreatic cysts are widely prevalent and commonly encountered in clinical practice. While prevalence according to imaging studies ranges between 2 and 15%, some autopsy data suggest a prevalence as high as 50% in aging populations [1, 2]. Even though the majority of pancreatic cystic lesions are intraductal papillary mucinous neoplasms (IPMNs) [3], with potential for malignant transformation, prospective follow-up data in a population-based setting suggest that most pancreatic cysts are harmless incidental findings [4].

IPMNs are intraductal epithelial neoplasms with potential for malignant transformation composed of mucin-producing columnar cells and may involve the main pancreatic duct (MPD) (MD-IPMN), the branch ducts (BD-IPMN), or both (mixed IPMN) [5]. The anatomical classification is important since it dictates the malignant potential: MD-IPMN has a markedly higher risk of high-grade dysplasia (HGD)/invasive carcinoma (IC) than BD-IPMN [6]. These lesions show papillary proliferation, cyst formation, and varying degrees of cellular atypia [7].

Most patients are asymptomatic, and diagnosis is incidental when imaging studies are requested due to unrelated indications [8]. A small number may complain of nonspecific symptoms such as nausea, vomiting, abdominal or back pain, and others may have pancreatitis-like symptoms and develop exocrine and endocrine pancreatic insufficiency due to obstruction of the MPD by mucin. Therefore, in cases of acute or chronic pancreatitis we must exclude the presence of IPMN as an etiological factor, although differential diagnosis is challenging, especially in patients with Wirsung duct ectasia [9]. Due to the insidious nature and

lack of awareness of the disease, there is often a delay in diagnosis of an IPMN in up to several months.

Since pancreatic cysts are common, the most important goal was to identify the small percentage of patients with high risk of developing a malignancy in the huge number of patients with presumed IPMNs, taking into account a healthcare economic perspective and the progressively older/frail population. For instance, 3.6 million dollars is spent on cyst surveillance for each cancer detected in the USA, without making appreciable change in cyst-related pancreatic adenocarcinoma mortality [10]. The increased detection and awareness of IPMNs led to the development of several consensuses and guidelines [5, 6, 11–13]. Although most of the data on IPMNs do not provide high-level evidence, the most recent guidelines are regarded as "evidence-based" [5, 11].

In this review, the Portuguese Pancreatic Club summarizes the risk assessment of a patient with an IPMN, focusing on the high-risk stigmata (HRSs)/worrisome features (WFs) or absolute/relative indications for surgery according to different guidelines. An updated perspective on the surveillance strategy for IPMNs is presented comparing the available evidence. A literature review was performed using PubMed with the search terms "intraductal papillary mucinous neoplasm," "surveillance," and "follow-up." The final manuscript was revised and approved by all members of the Governing Board of the Portuguese Pancreatic Club.

Risk Assessment

According to Fukuoka/Kyoto guidelines [5, 6], the predictive factors of HGD/IC in IPMNs have been called HRS/WF. Although HRSs are strong predictors of HGD/IC, they lack specificity, which reinforces that other factors such as patient's general condition, comorbidities, life expectancy, and preferences should be taken into account while addressing the decision of surgery [14]. The terms HRS/WF, used in Fukuoka/Kyoto consensus [5, 6], differ from the European guidelines, which consider instead the "absolute indication" and "relative indication" for surgery, as well as criteria for referral to multidisciplinary team meetings [11–13].

Table 1 compares HRS, absolute indications for surgery and for referral to multidisciplinary team meeting, according to the latest consensus and guidelines [5, 6, 11–13]. Obstructive jaundice is associated with HGD/IC with a sensitivity of 75–83% and a specificity of 61–65% [15]. Differentiating a mural nodule from a solid component is important since the former may indicate a noninvasive lesion and the last may point to IC or concomitant pancreatic ductal adenocarcinoma (PDAC). However, due to the difficulty in clinical practice to clearly distinguish them, both are considered HRS in the Fukuoka/Kyoto consensus. The cut-off value for the mural nodule (≥5 mm vs. ≥10 mm), as well as for the MPD dilation (≥5 mm vs. ≥10 mm), is still controversial [16]. Suspicious or positive cytology, if performed, may represent HGD/IC in 91–100% and 100%, respectively, but has low sensitivity [17].

Table 2 compares the WF, relative indications for surgery and consideration for referral to multidisciplinary team meeting, according to the latest consensus and guidelines [5, 6, 11–13]. As previously stated, the MPD obstruction due to viscous mucin secretion or MPD stenosis due to tumor involvement may cause acute pancreatitis, reported in up to 20% of patients with an IPMN [12]. However, larger series have pointed out that incidence of HGD/IC for patients with IPMNs and history of acute pancreatitis is similar in patients with IPMNs and low-grade dysplasia [18]. In case of repeated episodes of acute pancreatitis, surgery may be considered to improve quality of life [5]. Increased CA 19-9 is considered a good predictor of malignancy including PDAC and IPMN with HGD/IC and should prompt consideration for surgical therapy [19]. However, the current CA 19.9 cut-off was recently demonstrated to shorten surveillance intervals, cause unnecessary surgeries, and is not predictive of HGD/IC [20]. New onset/recent exacerbation of diabetes mellitus carries increased risk of HGD/IC and should be considered a WF according to Kyoto and European guidelines, highlighting the importance of HbA1c in surveillance [5, 11]. Thickened cyst walls, although without an evidenced-based cut-off to predict HGD/IC (one report proposed a 2.5-mm cut-off, with an odds ratio of 3.51 [21]), abrupt change in caliber of MPD with distal atrophy, lymphadenopathy, and cyst growth ≥2.5 mm/year are considered WFs (the last criteria changed with the recent guidelines vs. ≥5 mm/2 years in 2017 Fukuoka guidelines). It is worth mentioning that the greater the number of risk factors, the higher the probability of malignancy [22]. Indeed, the risk of HGD/IC increases in a stepwise fashion with the number of WF to 22, 34, and 59% with 1, 2, and 3 WF, respectively, reaching 100% in patients with 4 or more WF [5].

As stated before, MD-IPMNs carry a higher risk for malignant transformation and surgical fit patients should be referred for surgery. Since mixed-type IPMNs may behave in a similar fashion as MD-IPMNs, the same principle applies and patients should also be referred for surgery [5, 11]. Preoperative counseling is essential

Table 1. Indications for surgery (*AGA institute guideline*), absolute indications for surgery (*European evidence-based guidelines*), indications for referral to a multidisciplinary team meeting (*ACG clinical guideline*), and HRS (*Kyoto guidelines*) in a patient with IPMN

Indications for surgery (*AGA Institute Guideline 2015*)[a] [12]	Absolute indications for surgery (*European Evidence-Based Guidelines 2018*) [11]	Indications for referral to multidisciplinary team meeting (*ACG Clinical Guideline 2018*) [13]	High-risk stigmata (*Kyoto Guidelines 2024*) [5]
	Jaundice (tumor related)	Obstructive jaundice	Obstructive jaundice in a patient with cystic lesion of the head of the pancreas
	Enhancing mural nodule ≥5 mm	Mural nodule	Enhancing mural nodule ≥5 mm or solid component
Solid component	Solid mass	Solid mass	
MPD dilation ≥5 mm (on MRI and EUS)	MPD dilation ≥10 mm	Main duct involvement Patulous ampulla	MPD ≥10 mm
Positive cytology for malignancy	Positive cytology for HGD/ malignancy	Cytology with HGD or pancreatic cancer	Suspicious or positive (HGD or adenocarcinoma) cytology result (*added criteria since Fukuoka consensus*)

AGA, American Gastroenterological Association; ACG, American College of Gastroenterology; MPD, main pancreatic duct; MRI, magnetic resonance imaging. [a]According to AGA guidelines, positive cytology for malignancy and/or at least two high-risk features (cyst size >3 cm, MPD dilation ≥5 mm, or the presence of a solid component) are indications for surgery.

Table 2. Relative indications for surgery (*European evidence-based guidelines*), consideration for referral to a multidisciplinary team meeting (*ACG clinical guideline*) and worrisome features (*Kyoto guidelines*) in a patient with IPMN

Relative indications for surgery (*European Evidence-Based Guidelines 2018*) [11][a]	Consideration for referral to multidisciplinary team meeting (*ACG Clinical Guideline 2018*) [13][a]	Worrisome features[a] (*Kyoto Guidelines 2024*) [5]
Acute pancreatitis (caused by IPMN)	Concern for cystic neoplasm as a cause for acute pancreatitis	Acute pancreatitis
Increased serum levels of CA 19-9 (>37 U/mL)		Increased serum CA 19-9
New onset of diabetes mellitus		New onset/acute exacerbation of diabetes within past 1 year
Cyst diameter ≥40 mm[b]	*Cyst ≥30 mm*[b]	*Cyst ≥30 mm*[b]
Enhancing nodule <5 mm		Enhancing mural nodule <5 mm
		Thickened/enhancing cyst walls
MPD between 5 mm and 9.9 mm	MPD dilation ≥5 mm	MPD ≥5 mm and <10 mm
	Change in the main duct caliber with upstream atrophy	Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy
		Lymphadenopathy
Growth rate ≥5 mm/year[b]		*Cyst growth rate ≥2.5 mm/year*[b] (*updated criteria since Fukuoka consensus, which previously suggested cyst growth rate ≥5 mm/2 years*)

ACG, American College of Gastroenterology; MPD, main pancreatic duct. [a]Multiple risk factors have an addictive effect on the risk of high-grade dysplasia/invasive carcinoma. [b]Text in italic highlights differences between guidelines.

Table 3. Surveillance strategy for the non-resected IPMN according to the latest consensus and guidelines

Guideline/consensus	Timing of surveillance[a]	How to perform surveillance?
AGA Institute Guideline 2015 [12]	Cyst <30 mm without solid component or dilated pancreatic duct: follow-up in 1 year, then every 2 years for a total of 5 years	MRI
European Evidence-Based Guidelines[b] 2018 [11]	Cyst <40 mm: 6-month follow-up in the first year, followed by yearly follow-up when no risk factors are present that establish an indication for surgery	Clinical evaluation Serum CA 19-9 MRI and/or EUS
ACG Clinical Guideline 2018 [13]	Cyst <10 mm: follow-up in 2 years (×4 years) Cyst ≥10 mm and <20 mm: follow-up in 1 year (×3 years) Cyst ≥20 mm and <30 mm: follow-up in 6–12 months (×3 years)	MRI MRI MRI or EUS
Kyoto Guidelines 2024 [5]	Cyst <20 mm: 6 months once, then every 18 months if stable Cyst ≥20 mm and <30 mm: 6 months twice, then every 12 months if stable Cyst ≥30 mm without other worrisome feature: every 6 months	Clinical evaluation Serum CA 19-9 HbA1c MRI MDCT/EUS should be considered when changes are observed in the MRI

AGA, American Gastroenterological Association; ACG, American College of Gastroenterology; MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography; MDCT, multidetector computed tomography. [a]If there is IPMN progression, careful reassessment of high-risk stigmata/worrisome features/indications for surgery is mandatory. [b]For patients with relative indication for surgery, the elderly and those with severe comorbidities, a 6-month follow-up is recommended.

discussing surgical options with the patient ranging from radical pancreatectomy with lymphadenectomy if IC is suspected to organ-preserving techniques if noninvasive lesion is considered [5].

Surveillance of Non-Resected IPMNs

The "dual carcinogenesis" is a key concept during management of IPMNs, as cancer may occur either from progression of IPMN to HGD/IC (IPMN-derived carcinoma) or from development of PDAC apart from IPMN in the same pancreas (concomitant PDAC). In non-resected IPMNs, clinicians should bear in mind that cumulative incidence of transformation of indolent BD-IPMN to HGD/IC is 0.94–3.3% by 5 years, 2.3–6.6% by 10 years, and 7.6–15% by 15 years [5], although the risk is lower than previously considered [23]. The most important risk factors for IPMN-derived carcinoma are cyst size and MPD diameter at diagnosis, although these factors were not associated with the risk of concomitant PDAC [24]. Table 3 highlights the surveillance strategy for the non-resected IPMNs according to the latest consensus and evidence-based guidelines, regarding timing and the proposed method [5, 6, 11–13].

Multifocal BD-IPMNs are reported in around 20–40% of the patients [6], and the majority of these lesions arise independently ("field defect theory"). Multifocality is not a criterion for considering increased risk for HGD/IC [25, 26]. In this regard, management should be dictated by the lesion having the highest risk, either if indication for surgery or surveillance [5].

One important aspect of non-resected IPMNs is when clinicians should/may stop surveillance. Life-long surveillance is associated with a significant healthcare expenditure and psychological burden for the patient/physician [27]. Although finding appropriate criteria to decide surveillance discontinuation is important, clinicians should bear in mind that risk of concomitant PDAC remains even after a 5-year follow-up [28]. The risk of concomitant PDAC is about 3- to 5-fold higher comparing with age-matched population [28], and all these facts must be discussed with the patient before deciding to stop surveillance. Moreover, some patients with contraindications for surgery may be considered candidates for endoscopic ultrasonography-guided ablation therapy, and this might influence the decision to continue/stop surveillance [29]. Table 4 includes proposed criteria to consider stopping surveillance, according to different guidelines/consensuses. Ideally,

Table 4. Criteria for considering stopping surveillance according to different consensuses/guidelines

Guideline/consensus	Criteria for considering stopping surveillance
AGA Institute Guideline 2015 [12]	No significant change in the characteristics of the cyst after 5 years Unfit for surgery
European Evidence-Based Guidelines 2018 [11]	Unfit for surgery
ACG Clinical Guideline 2018 [13]	Assess utility in those aged >75 years Unfit for surgery
Kyoto Guidelines 2024 [5]	Unchanged BD-IPMN <20 mm during a 5-year period Stable cyst <30 mm in individuals ≥75 years old during a 5-year period Cyst <15 mm in individuals >65 years old Unfit for surgery Life expectancy <10 years

AGA, American Gastroenterological Association; ACG, American College of Gastroenterology.

surveillance of presumed BD-IPMN should be safely discontinued in selected patients once their risk of malignancy is similar to the risk of age-matched general population [23].

Extra-Pancreatic Neoplasms

In patients with IPMNs, extra-pancreatic neoplasms are reported in up to 30% [5]. Most of them are diagnosed during initial assessment or after resection of extra-pancreatic neoplasms, but in the remaining patients, extra-pancreatic neoplasms may be diagnosed during IPMN surveillance [30]. The distribution of involved organs depends on ethnicity and country. In the Western world, skin, breast, kidney, and prostate are frequent malignancies associated with IPMN, in contrast with Asian countries, with a higher prevalence of gastrointestinal cancers [31]. Despite this, recent evidence suggests that incidence of extra-pancreatic neoplasms in patients with IPMNs is similar compared with population-based incidence of each country [32]. No additional screening besides the national protocols regarding extra-pancreatic neoplasms is necessary in patients with IPMNs.

Comparison between Guidelines

As previously stated, there are several published national and international guidelines, mainly consensus based. Currently, the 2015 American Gastroenterological Association (AGA) [12], the 2018 European Study Group on Cystic Tumors of the Pancreas [11], the 2018 American College of Gastroenterology (ACG) [13], and the 2024 International Association of Pancreatology (IAP) [5] provide recommendations on follow-up concerning the risk of malignancy.

Due to the complex and indolent nature of the disease, the primary goal when discussing IPMN surveillance is to find the balance between the risk of malignant progression and overtreatment. Tables 1–3 highlight small but important differences concerning high-risk features for HGD/IC, timing and method of surveillance, as well as factors that may result in follow-up discontinuation.

For IPMNs, the IAP and European guidelines suggest resection when the MPD is involved (MPD ≥10 mm; or in cases of mixed-type IPMN). In contrast, according to AGA recommendations, the presence of a mural nodule or positive cytology for malignancy is a necessary condition. Management of BD-IPMN differs between guidelines, raising concerns about which one has the better diagnostic accuracy.

In a monocentric retrospective cohort, the AGA 2015/IAP 2017/European Guidelines 2018 were compared to evaluate the diagnostic accuracy in identifying advanced neoplasia in patients with IPMNs [33]. The AGA guidelines were found to have a lower sensitivity (27%), with the risk of missing advanced neoplasia in 26%, compared with 2.1% and 1.4% with the IAP and European recommendations, respectively. In this regard, the IAP and European guidelines are associated with higher rates of unnecessary surgery (83% and 76%) against 8.6% in the AGA recommendations. Other studies have demonstrated a missed rate of advanced neoplasia in 12–93% when applying the AGA guidelines [34–36]. Considering the 2017 IAP guidelines, the HRS was associated with 90% sensitivity and 67% specificity for identifying advanced neoplasia in IPMN [37]. One multicenter study demonstrated that the

accuracy of the 2018 European guideline was 65% when ≥1 relative indication was present [38]. Due to the novelty of the Kyoto guidelines from 2024 [5], no study has so far assessed the diagnostic accuracy in detecting advanced neoplasia in IPMNs.

From the authors' perspective, we tend to follow the IAP guidelines with the definition of HRS/WF to guide for resection, to maintain surveillance according to the cyst size or to consider discontinuing follow-up if criteria proposed by the same group are met. However, clearly new diagnostic approaches are needed to more accurately identify high-risk patients. Next-generation sequencing of cyst fluid, with some promising results [39], multimodality tests that evaluate clinical features, imaging characteristics, genetic and biochemical markers [40], or even artificial intelligence-based clinical decision-making [41] may complement our clinical practice with the aim of improving future outcomes.

Conclusions/Key Points

- Most of the current guidelines have a low malignancy miss rate with the cost of surgical overtreatment.
- According to 2024 Kyoto Guidelines, the HRS and WF should be searched as potential indications for surgery, especially if multiple WFs are present.
- Surveillance of a non-resected IPMN depends on the cyst size and is mainly performed with clinical evaluation, CA 19-9, HbA1c, and magnetic resonance imaging; endoscopic ultrasonography should be considered if there are changes in other imaging methods, especially if fine-needle aspiration may modify management.
- Multidisciplinary management preferably in reference centers is of utmost importance given the indolent and complex nature of the disease.
- A global evidence-based guideline that combines the several guideline groups is mandatory to uniformize care.

Statement of Ethics

Due to the nature of the article, ethical approval was not required.

Conflict of Interest Statement

Miguel Bispo is a member of the Editorial Board of *GE – Portuguese Journal of Gastroenterology* journal; Eduardo Rodrigues-Pinto is an associated editor of *GE – Portuguese Journal of Gastroenterology* journal. Francisco Vara-Luiz, Alexandra Fernandes, Filipe Vilas-Boas, Tiago Cúrdia-Gonçalves, and Pedro Pinto-Marques have no personal conflicts of interest or financial relationships relevant to this publication to declare.

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Author Contributions

Francisco Vara-Luiz and Pedro Pinto-Marques: article conception and design, literature review, and draft of the manuscript. Alexandra Fernandes, Miguel Bispo, Filipe Vilas-Boas, Tiago Cúrdia-Gonçalves, and Eduardo Rodrigues-Pinto: literature review and critical review of the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

All the data analyzed during this review are included in this article. Further inquiries can be directed to the corresponding author.

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