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Intraductal Papillary Mucinous Neoplasms (IPMN): Diagnosis, Classification, and Risk Assessment - A Review of Current Medical Knowledge

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ABSTRACT

Introduction

In recent years, the widespread utilisation of advanced imaging modalities has led to a surge in the detection rate of pancreatic cystic lesions, particularly intraductal papillary mucinous neoplasms (IPMN). Consequently, this review aims to provide a comprehensive examination of IPMN, focusing on elucidating its intricate facets including definition, epidemiology, pathogenesis, classification, imaging modalities for diagnosis, analysis of pancreatic cyst fluid, evaluation of malignant potential, and identification of pertinent features.

Brief Overview of Current Knowledge:

IPMN represents a diagnostic conundrum owing to its variable biological behaviour encompassing both benign and malignant spectra, necessitating meticulous evaluation and risk stratification. Various imaging techniques such as MRI, CT, EUS and abdominal ultrasonography serve pivotal roles in the diagnostic algorithm and risk assessment of IPMN. Additionally, the analysis of pancreatic cyst fluid, incorporating biomarkers and the string sign test, assumes a critical role in discerning mucinous from non-mucinous cysts and gauging malignant potential. Discriminating high-risk stigmata and worrisome features serve as a compass for clinical decision-making regarding the imperative of surgical intervention versus vigilant surveillance.

Summary

Despite persistent challenges, the ongoing evolution of diagnostic modalities and risk assessment methodologies augur well for refining therapeutic strategies and enhancing clinical outcomes in managing IPMN. This review underscores the imperative of sustained research endeavours in the realm of pancreatic oncology to enrich our comprehension of IPMN pathophysiology and to optimise clinical care paradigms.

KEYWORDS: Pancreatic Cyst; Pancreatic Intraductal Neoplasms; Diagnostic Imaging; Risk Assessment; EUS-FNA; Pancreatic Neoplasms

DEFINITIONS OF ABBREVIATIONS

CT - Computed Tomography

MRI - Magnetic Resonance Imaging

EUS - Endoscopic Ultrasound

IPMN - Intraductal Papillary Mucinous Neoplasms

MD-IPMN - Main Duct Intraductal Papillary Mucinous Neoplasms

BD-IPMN - Branch Duct Intraductal Papillary Mucinous Neoplasms

DECT - Dual-Energy Computed Tomography

WHO - World Health Organization

CA 19-9 - Cancer Antigen 19-9

CEA - Carcinoembryonic Antigen

FNA - Fine Needle Aspiration

HGD - High-Grade Dysplasia

IC - Invasive Carcinoma

HRS - High-Risk Stigmata

WF - Worrisome Features

GRE - Gradient Refocused Echo

FSE - Fast Spin Echo

T - Tesla

NGS - Next-Generation Sequencing

MCN - Mucinous Cystic Neoplasms

PDAC - Pancreatic Ductal Adenocarcinoma

MPD - main pancreatic duct MPD

INTRODUCTION

The widespread utilisation of advanced imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS), has led to a significant increase in the detection of pancreatic cysts, with a prevalence ranging from 2.4% to 19.6% [1, 2]. This surge in detection, particularly among older adults, with nearly 40% of individuals over 60 affected, underscores the growing clinical significance of pancreatic cysts and the need for a comprehensive understanding of their management [2]. Among these cystic lesions, intraductal papillary mucinous neoplasms (IPMN) are complex

and challenging, demanding in-depth knowledge and expertise from medical professionals, especially those dealing with older patients. This article aims to provide a comprehensive overview of IPMN, ensuring you are well-equipped to manage this challenging entity confidently.

IPMNs present a unique diagnostic dilemma due to their ability to exhibit both benign and malignant characteristics, with the potential for malignant transformation posing a significant threat to patient well-being [22]. This inherent complexity necessitates meticulous evaluation and careful decision-making regarding treatment strategies. The differentiation between benign and malignant IPMN further complicates the diagnostic process, often requiring additional diagnostic and therapeutic interventions [42]. Medical professionals must know this potential threat and act accordingly in their management strategies.

Despite these challenges, IPMNs offer medical professionals an exciting opportunity to advance their understanding of pancreatic neoplasia, refine diagnostic skills, and develop practical management approaches. Delving into the intricacies of IPMN can stimulate intellectual curiosity, push the boundaries of medical knowledge, and ultimately improve patient outcomes. This field is challenging and ripe for exploration, offering a pathway for significant professional growth and contribution to the medical community.

Given the complexities and implications of IPMN, particularly in light of the increasing incidence of pancreatic cysts and their impact on patient well-being, this article provides a comprehensive overview of the disease. The discussion primarily focuses on the foundational principles, equipping medical professionals like you with the knowledge and tools to manage this challenging entity confidently. Your role in understanding and managing IPMN is crucial, and this article aims to empower you in this process. While treatment strategies and surveillance protocols for IPMN are essential considerations, they will be addressed separately in subsequent articles, as this topic warrants a dedicated discussion due to its complexity.

THE GENESIS AND ESSENCE OF IPMN

Definition

Intraductal papillary mucinous neoplasm (IPMN) is a premalignant condition of the pancreas characterised by an abnormal growth of mucin-secreting cells within the pancreatic ductal system. This abnormal growth results in the formation of papillary projections, inducing cystic dilatation of the ducts and subsequent development of tumours [2, 3]. Notably, communication between these cystic formations and the pancreatic ductal network is a distinguishing feature of IPMN, setting it apart from other cystic lesions of the pancreas. IPMN displays a diverse natural history, encompassing slow-growing, localised lesions to invasive and metastatic tumours [4].

Epidemiology

IPMN exhibits a diverse natural course, ranging from slow-growing, localised lesions to invasive and metastatic tumours. However, accurately determining the prevalence of IPMN in the general population remains challenging, likely due to factors like asymptomatic lesions and limitations in diagnostic techniques [8, 9]. The potential for malignant transformation in IPMN highlights the importance of promptly and effectively comprehending and managing this condition.

Pathogenesis and aetiology

The pathogenesis of IPMN remains a multifaceted subject, albeit needs to be more clearly elucidated. Genetic mutations affecting genes such as GNAS, KRAS, and TP53 are critical drivers in IPMN pathogenesis [8-11]. These mutations cause an increase in mucus production by pancreatic epithelial cells, leading to the formation of the characteristic intraductal papillary structures emblematic of IPMN [12]. Subsequently, the pancreatic ductal system undergoes dilatation and cystic transformation. This progressive sequence of events can catalyse the transition of IPMN to pancreatic adenocarcinoma, a process characterised by a continuum from benign cystic lesions to aggressive malignancy [13]. Genetic mutations, augmented mucus secretion, and structural remodelling of the pancreatic ductal architecture converge as crucial mechanistic drivers in the pathogenesis of IPMN, ultimately culminating in the development and progression of pancreatic neoplasms [14].

Predisposing Risk Factors

Given the intricate interplay of various factors, thoroughly investigating the predisposing risk factors associated with IPMN is imperative. Clinical conditions such

as diabetes (particularly with insulin therapy), chronic pancreatitis, and a family history of pancreatic malignancies hold potential significance [21]. The link between tobacco smoking and IPMN remains inconclusive, but it may still potentially increase the risk of cancer development [15, 16]. It is important to note, however, that tobacco smoking is a well-established risk factor for pancreatic cancer. Genetic disorders, such as McCune-Albright syndrome [18], may also predispose individuals to develop IPMN through mutations in the GNAS gene [12, 19]. Additionally, there is an indication of an inherited predisposition to IPMN, underscoring the necessity for further scientific inquiry to enhance our understanding of this phenomenon [20].

CLASSIFICATION

Diverse classifications delineating IPMN are employed in contemporary clinical practice, and in this chapter, we shall deliberate on the foremost ones pertinent to clinical decision-making.

IPMN classification based on the localisation of cysts relative to the pancreatic ducts

This chapter will discuss the fundamental classification of IPMN, which delineates three principal categories based on the localisation of cysts relative to the pancreatic ducts [24]. This classification system, rooted in aetiology, comprises main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), and mixed-type IPMN (Fig.1). MD-IPMN involves alterations within the primary pancreatic duct. At the same time, BD-IPMN manifests in the smaller branches of the pancreatic duct. Mixed-type IPMN exhibits features of both the main and branch pancreatic ducts. The designation of mixed-type IPMN is established upon meeting two criteria: involvement of branch ducts (IPMN-BD) and dilation of the primary pancreatic duct exceeding 6 mm [2]. Notably, the detection of changes in the primary duct on pre-operative imaging suggests a more aggressive course, with up to 60% of cases undergoing resection for MD-IPMN demonstrating either in situ or invasive carcinoma. Conversely, malignancy is reported in 12–30% of resections for BD-IPMN [9]. However, the risk of malignancy in BD-IPMN is lower due to the selection bias inherent in surgical intervention, as resection is typically only performed in cases with the most concerning features [22].

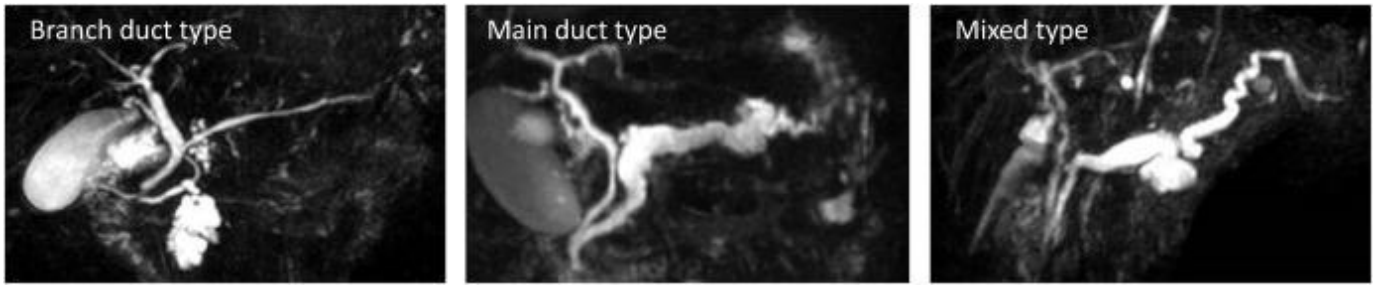

Fig. 1. Classification of IPMN on MRCP. The original photo was downloaded on 17.04.2024 [76].

Histopathological Classification

The Baltimore consensus classification is currently the preferred system for histopathological IPMN assessment – the former three-tiered classification aimed to precisely categorise the degree of dysplasia [23]. However, the clinical significance of IPMN with low-to-moderate dysplasia is now being reevaluated. With the increasing detection of IPMN cases exhibiting low or moderate dysplasia, non-operative observations suggest a minimal risk of progression to invasive carcinoma. Consequently, a two-tier classification system–low-grade and high-grade dysplasia (Fig.2) – has been proposed to better reflect practical clinical considerations [23]. This simplified system relies solely on histological evaluation of the highest grade of architectural and cytological atypia within the preneoplastic lesion.

Introducing this new dysplasia classification for IPMN promises to improve our understanding of the disease and facilitate more precise therapeutic decisions. Furthermore, it emphasises the need for additional investigations to determine the long-term efficacy of this classification system and its impact on patient outcomes [11, 23].

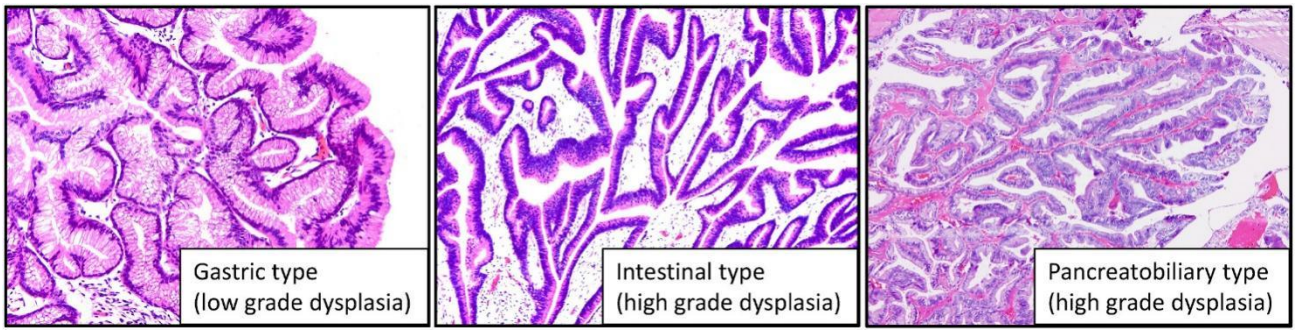

Fig. 2 The morphological findings of IPMN. The original photo was downloaded on 17.04.2024 [76]. Left; gastric type with low grade dysplasia. Middle; intestinal type with high grade dysplasia. Right; pancreatobiliary type with high grade dysplasia. (x20, Hematoxylin and eosin staining).

Histological Subtypes

IPMN can be further classified into histological subtypes based on the microscopic appearance of the papillae, which significantly correlates with their biological behaviour [13, 22]. These subtypes include gastric foveolar type, intestinal, pancreaticobiliary, and the recently described intraductal oncocytic papillary subtype.

One subtype, the **gastric foveolar-type IPMN** (Fig.2), resembles gastric epithelium, distinguished by abundant cytoplasmic mucin and basally located nuclei. Typically presenting as low-grade lesions [23, 27], gastric foveolar-type IPMN primarily occurs in branch duct IPMN. Additionally, cells of this type of IPMN overexpress gastric-type mucins MUC5AC and MUC6 [26]. In contrast to the gastric foveolar type, the **intestinal-type IPMN** (Fig.2) comprises long finger-like projections lined by mucin-producing epithelial cells resembling villous adenoma [29]. These types usually exhibit moderate to high-grade dysplasia and are predominantly observed in central duct IPMN. Intestinal-type IPMN excessively express MUC5AC, MUC2 and weakly MUC6. Invasive tumours associated with the intestinal type typically manifest as colloid carcinomas, which generally have a better prognosis. Another subtype, the **pancreaticobiliary-type IPMN** (Fig.2), resembles cholangiopapillary neoplasms.

It is characterised by more atypical neoplastic cells with less mucin and usually high-grade lesions [28]. **Intraductal oncocytic papillary neoplasms** are rare tumours characterised by characteristic neoplastic cells with eosinophilic cytoplasm due to an abundance

of mitochondria. Invasive tumours from this subtype may demonstrate characteristic oncocytic cytology, and genetic studies suggest a lack of Kras mutations typical of glandular carcinoma [30, 31].

Malignant Transformation

IPMN predisposes the development of two main types of malignant tumours: **colloid adenocarcinoma and tubular adenocarcinoma** [32, 33]. Colloid adenocarcinoma is characterised by sizeable extracellular mucin pools containing relatively small clusters of neoplastic cells. It typically develops against the background of the intestinal subtype of IPMN, and recent studies report significantly better outcomes in patients undergoing resection for colloid adenocarcinoma. On the other hand, tubular adenocarcinoma resembles conventional infiltrating ductal adenocarcinoma, characterised predominantly by tubular neoplastic glands associated with desmoplastic stroma. This type of adenocarcinoma associated with IPMN usually develops against the background of the pancreaticobiliary subtype of IPMN, and patients with IPMN-associated tubular adenocarcinoma have significantly worse 5-year survival rates (24%–50%) compared to colloid adenocarcinoma (70%–83%) [14, 32, 33].

IMAGING DIAGNOSIS

This chapter will delve into the diagnostic methods for identifying IPMN, particularly emphasising the precision and reliability of high-resolution imaging and endoscopy [34]. These methods allow for the identification of IPMN through the appearance of significant dilatation of the pancreatic duct or multiple cysts, as well as dilated branches of the main duct. The distribution of these changes is diverse, with approximately 50% developing in the head of the pancreas, 7% in the tail, 4% in the uncinate process, and the remaining 39% scattered throughout the pancreas [2]. The diagnostic focus for IPMN is threefold: differentiating IPMN from other pancreatic cysts, classifying types of IPMN, and identifying features suggestive of neoplastic changes [35, 36, 37]. It is important to note that in most patients with IPMN, the course of the disease is asymptomatic, and symptoms may only arise due to complications such as pancreatitis or ductal obstruction [38,39,40]. However, these changes are often detected incidentally during routine imaging studies such as CT and MRI [41].

Magnetic Resonance Imaging (MRI)

It is recommended that the initial evaluation of the lesion be conducted using pancreatic and biliary tract MRI to avoid exposure to X-ray radiation, which is particularly important for elderly patients or those with existing comorbidities [2, 34]. MRI protocols typically involve using a device with a magnetic field of at least 1.5 Tesla (T) equipped with phased-array coils. The recommended sequences include T1-weighted gradient-echo (GRE) sequences during inspiration and expiration, T2-weighted single-shot fast spin echo (FSE) sequences,

and dynamic T1-weighted spoiled GRE sequences before and after intravenous gadolinium contrast administration [42]. MRI protocols without intravenous contrast can monitor pancreatic cystic changes, reducing examination time and minimising the risk of complications [43, 44, 45, 46]. Additionally, contrast-enhanced imaging may benefit initial lesion characterisation and risk stratification, allowing for a more precise assessment of the entire pancreas, especially in patients at high risk of developing pancreatic cancer [47, 48].

Multidetector Computed Tomography (MDCT)

Multidetector computed tomography (MDCT) of the pancreas offers a valuable alternative to magnetic resonance imaging, particularly for patients with contraindications to MRI. It provides advantages such as easier access, high resolution, and the ability to generate multiplanar reconstructions [49, 50]. The recommended MDCT pancreatic examination protocol involves dual-phase contrast acquisitions in the pancreatic and portal venous phases using a narrow detector configuration [49, 50]. Some institutions utilise the double bolus technique and dual-energy CT systems in MDCT, achieving comparable visualisation of the pancreatic parenchyma and tumours with a lower radiation dose [49, 50]. Multiplanar reconstructions and maximum intensity projections of 1-3 mm slices aid in detecting duct communication and characterising pancreatic cysts [51, 52]. While contrast-enhanced CT is essential, dual-energy computed tomography (DECT) or spectral CT can improve lesion clarity and differentiate between cystic and solid lesions with a reduced radiation burden [53]. In summary, a dual-phase CT examination is recommended for initial assessment, with the option of repeating the dual-phase protocol for monitoring. However, single acquisitions during the early portal vein phase or DECT in the portal vein phase are also considered acceptable options [49, 50, 53].

Abdominal Ultrasonography

Ultrasound offers a convenient and cost-effective alternative to MRI and computed tomography CT, particularly for patients with contraindications to these modalities. It is a tool that can effectively monitor significantly larger pancreatic cysts. Research has shown that ultrasound can detect cysts with a diameter above 2 cm, achieving a sensitivity of up to 78%, and for those larger than 3 cm - 100% [54]. Furthermore, there's a positive correlation between patient characteristics such as smaller body size, body mass index, and gender and the ability to visualise cysts. Cysts were more frequently observed in women, possibly related to these anatomical factors. However, subcutaneous or visceral fat content, which was not explicitly addressed in these studies, may also influence the results [54].

One study by Jeon et al. [55] involving a sample of 938 patients with 1064 cysts found a cyst detection rate of 88.3%, with a median diameter of detected cysts of 13 mm compared to 10 mm for undetected cysts. These results suggest that cyst detection is significantly higher when abdominal ultrasonography is performed following other imaging modalities, especially for smaller cysts with a diameter of less than 25 mm [55].

It is essential to consider that despite promising findings, further research is required to validate the efficacy of ultrasound in monitoring pancreatic cysts. Contrast-enhanced ultrasonography may be particularly beneficial for patients who cannot receive intravenous contrast agents based on iodine or gadolinium, as it could help distinguish soft cyst wall nodules from mucus and guide precise biopsies [56]. However, in the USA, access to contrast agents for ultrasonography is limited, and the skills required to perform these procedures need further development. While these methods hold promise, additional research is crucial to establish their definitive clinical value.

Endoscopic Ultrasound (EUS)

Endoscopic ultrasound (EUS) is a valuable follow-up diagnostic method when results from CT and MRI are inconclusive [4]. Despite being operator-dependent and invasive, EUS offers the unique advantage of fine needle aspiration to analyse cyst fluid [38, 39, 40].

EUS-FNA is crucial in distinguishing between mucinous and nonmucinous cysts, evaluating duct communication, and guiding cytology, molecular analysis, and biomarker evaluation for cyst characterisation [31]. EUS should be strongly considered in cases with suspicious features on MRI or CT or if the patient presents with concerning symptoms, as it can significantly aid in distinguishing neoplastic from non-neoplastic cysts [38, 52, 57]. Although

fluid analysis obtained through EUS-FNA allows for examining tumour markers and genetic mutations, the sensitivity for cancer detection remains limited [58]. However, studies have consistently shown that EUS offers greater accuracy than CT and MRI in detecting concerning features suggestive of malignancy in cystic pancreatic masses [58, 59]. EUS with contrast enhancement can also be helpful for cyst characterisation and guiding biopsies [60]. The safety of pancreatic cyst puncture using EUS has been well-established. New technology allows for direct cyst wall biopsy using micro forceps, which may provide more accurate cyst characterisation and subtyping information than traditional cytology [61, 62].

ANALYSIS OF PANCREATIC CYST FLUID: A MULTIFACETED APPROACH

Accurate identification of pancreatic cysts is crucial for optimal patient management and treatment, ultimately preventing unnecessary surgical interventions. The most common potentially malignant pancreatic cysts include IPMN and mucinous cystic neoplasms (MCN). Distinguishing between mucinous and nonmucinous cysts is fundamental for pancreatic cyst diagnosis, with crucial information provided by EUS-FNA [66, 67, 68]. Fluid analysis of pancreatic cysts includes assessing CEA (carcinoembryonic antigen) concentration, amylase activity, fluid cytology, and the string sign test [103].

The String Sign Test: A Simple Yet Valuable Tool

The string sign test, a non-invasive procedure performed following fine-needle aspiration during endoscopic ultrasound, is a valuable tool for diagnosing mucinous pancreatic cysts. The test involves observing the flow characteristics of cyst fluid as it exits the EUS-FNA needle. A positive test result signifies the presence of a string-like structure in the fluid, measuring at least 1 cm in length and persisting for at least 1 second without disruption. While the dynamic nature of the test limits the measurement of the string’s exact dimensions, a single positive result is considered diagnostic due to the uneven distribution of mucus within the cyst fluid. The test is not performed in cases of bloody cyst fluid, as clots may cause false-positive results [73].

Beyond the String Sign: Exploring a Spectrum of Biomarkers

In addition to the string sign test, the evaluation of pancreatic cyst fluid encompasses a range of biomarkers to enhance diagnostic accuracy. Carcinoembryonic antigen is currently

the most established marker, with elevated levels in cyst fluid associated with mucinous cysts. However, research is ongoing to identify even more effective markers. Glucose concentration in cyst fluid is a promising alternative to CEA, offering simplicity, speed, and cost-effectiveness advantages while demonstrating comparable sensitivity and specificity [63, 64].

Amylase/lipase levels can also help exclude pseudocysts (amylase <250 U/L; sensitivity 0.44, specificity 0.98) but do not allow differentiation between other cyst types [71, 72]. For IPMN specifically, serum cancer antigen (CA 19.9) may be considered, particularly if malignant transformation is suspected [64, 65, 66]. An increased CA 19.9 concentration > 37 j/ml in serum may indicate malignant transformation within IPMN [2].

DNA markers, especially mutations in the GNAS and KRAS genes, hold promise for identifying mucin-producing pancreatic cysts. When the diagnosis remains unclear and has treatment implications, these mutations can be analysed using advanced techniques such as next-generation sequencing (NGS) [67, 68, 69, 70].

Conclusion

The analysis of pancreatic cyst fluid has evolved into a multifaceted approach, incorporating physical characteristics like the string sign test alongside a growing array of biochemical and molecular markers. This comprehensive evaluation plays a vital role in differentiating cyst types, guiding treatment decisions, and improving patient outcomes.

EVALUATION OF MALIGNANT POTENTIAL IN IPMN

According to the 2012 guidelines, factors predictive of high-grade dysplasia (HGD) or invasive carcinoma (IC) in IPMN are classified as high-risk stigmata (HRS) and worrisome features (WF) [74]. While HRS strongly suggest an elevated risk of HGD/IC, their specificity is not ideal. Recommendations emphasise careful consideration of surgical necessity, accounting for the suspicion of HGD/IC and the patient's overall health status, comorbidities, life expectancy, and preferences. Therefore, "HRS" and "WF" are the preferred terms over "absolute indications" and "relative indications" in surgical decision-making [75]. Concluding the chapter, a comparative table (Table 1) of HRS and WF is provided.

High-Grade Dysplasia/Invasive Carcinoma (HGD/IC)

Intraductal papillary mucinous neoplasms are a group of pancreatic cysts that occasionally progress to high-grade dysplasia or invasive carcinoma (HGD/IC). Mechanical jaundice, a symptom of bile duct obstruction, is a rare occurrence in IPMNs but strongly suggests the presence of HGD/IC [76].

Mechanical Jaundice and HGD/IC in IPMNs

Mechanical jaundice, characterised by yellowing of the skin and eyes, occurs when bile flow is impeded, causing bile to accumulate in the bloodstream. In IPMNs, mechanical jaundice is a significant risk factor for HGD/IC, with a sensitivity ranging from 75% to 83% and specificity around 61% to 65% [77, 78, 79]. The presence of mechanical jaundice in IPMNs warrants prompt evaluation and intervention to address the underlying HGD/IC.

Distinguishing Wall Nodules from Solid Components in IPMNs

IPMNs can exhibit two distinct morphological features: wall nodules and solid components. Wall nodules are protrusions on the cyst wall, typically indicating a non-invasive change [76]. In contrast, solid components, defined as solid masses within the pancreatic parenchyma, suggest the presence of IPMN with HGD/IC or concurrent pancreatic ductal adenocarcinoma (PDAC) [35, 75]. Distinguishing between wall nodules and solid components can be challenging in clinical practice, and both are considered high-risk alterations [35, 75].

Diagnosing HGD/IC in IPMNs: The Role of Wall Nodules and MPD Dilatation

Evaluating wall nodules and main pancreatic duct dilatation is crucial in diagnosing HGD/IC in IPMNs. The height of a wall nodule is typically assessed using EUS, while multidetector computed tomography/magnetic resonance imaging provides the maximum diameter [80]. The threshold size of a wall nodule for diagnosing HGD/IC remains a topic of debate, with some guidelines suggesting a cutoff of ≥5 mm [35, 75]. However, the presence of a wall nodule alone does not always significantly impact the prediction of HGD/IC [80, 81, 82]. In addition to wall nodule size, MPD dilatation is another critical consideration. MPD dilatation ≥5 mm is classified as a problematic feature (WF), while a wall nodule ≥10 mm is considered a high-risk stigma (HRS) [35, 76]. However, due to insufficient evidence supporting these revisions, the current guidelines maintain that a wall nodule ≥5 mm and MPD ≥10 mm remain classified as HRS [35, 76]. Conversely, a wall nodule <5 mm and MPD ≥5 mm and <10 mm are categorised as WF, consistent with previous guidelines from 2017 [35].

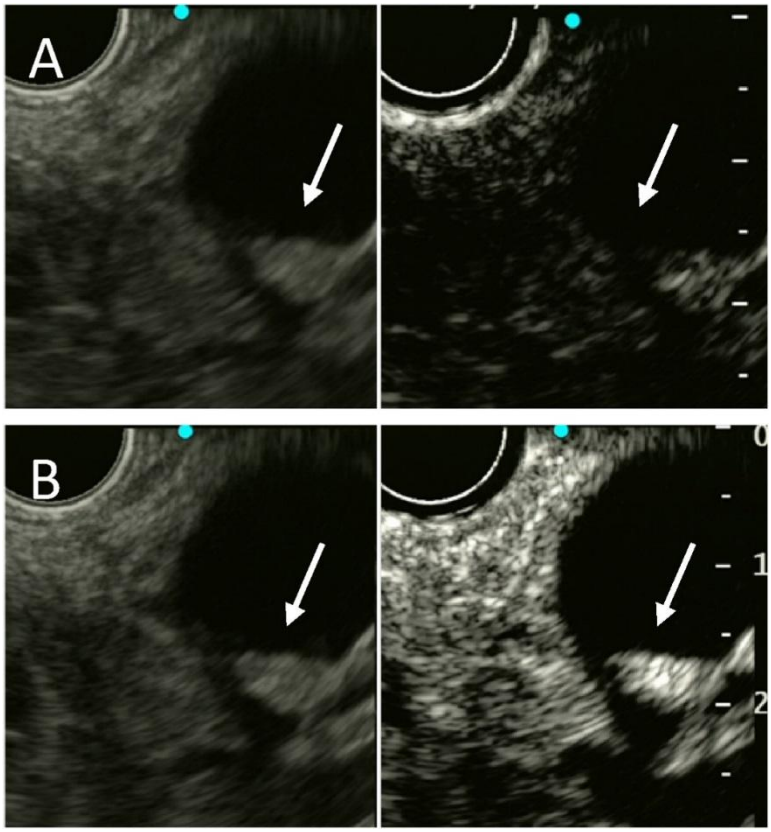

Fig.4. Endoscopic ultrasound detected a mural nodule. The original photo was downloaded on 17.04.2024 [76].

A. Findings before isoniazid injection. The arrow indicates a mural nodule.

B. Contrast-enhanced finding after isoniazid injection. An enhanced mural nodule (arrow) can be detected.

Cytological Grading and Risk of HGD/IC in IPMNs

Based on the World Health Organization (WHO) classification, cytological grading provides valuable prognostic information regarding the risk of HGD/IC in IPMNs [83]. "Suspicious" and "positive" cytological results are associated with HGD/IC risks of 91-100% and 100%, respectively, and are therefore considered HRS [83]. Pre-operative cytological diagnosis of IPMNs enhances the accuracy of risk assessment and clinical management, guiding treatment decisions for patients with pancreatic cysts [83, 84].

Mechanical jaundice, wall nodules, solid components, and cytological grading are critical diagnostic factors for HGD/IC in IPMNs. Early identification and intervention for these high-risk features are essential for improving patient outcomes. Prompt evaluation of

IPMNs with mechanical jaundice, thorough imaging assessment of wall nodules and MPD dilatation, and cytological analysis are crucial steps in the diagnostic workup for HGD/IC.

Worrisome Features (WFs) and Their Prognostic Significance

Worrisome features (WFs) are clinical or radiological characteristics associated with an increased risk of HGD/IC in IPMNs. This review summarises the key WFs and their prognostic significance in IPMNs.

Acute Pancreatitis

Acute pancreatitis is a potentially severe complication of IPMN resection, occurring in approximately 20% of patients [85, 86]. The incidence of acute pancreatitis is reportedly higher in patients with IPMNs harbouring advanced dysplasia (HGD/IC) compared to those with mild dysplasia [82, 87]. The mechanisms underlying acute pancreatitis in IPMNs include ductal obstruction caused by dense mucus plugging or direct tumour compression [85, 86].

Elevated Serum CA19-9 Levels

Elevated serum levels of CA19-9, a tumour marker, are often associated with various gastrointestinal malignancies, including pancreatic cancer. In IPMNs, elevated CA19-9 levels (>37 U/L) demonstrate moderate sensitivity (41%-74%) but high specificity (85%-96%) for predicting HGD/IC [66, 80, 81, 88, 89].

New-onset or Worsening Diabetes

The development or worsening of diabetes within the past year in approximately 25% of IPMN patients is associated with an increased risk of HGD/IC and pancreatic cancer [90, 91, 92, 93, 94]. This association may be related to shared underlying mechanisms involving pancreatic inflammation and alterations in glucose metabolism.

Cyst Wall Changes

An increase in cyst wall nodule diameter of less than 5 mm and thickening/enhancement of cyst walls may suggest an increased risk of malignancy. However, cyst wall thickening/enhancement is a subjective finding, and precise measurement methods or cutoff values are yet to be established. Studies suggest that septal thickness measured by EUS may be a helpful risk indicator for HGD/IC, comparable to cyst wall nodule size [95].

Sudden Pancreatic Duct Changes

Pancreatic duct diameter, characterised by distal pancreatic atrophy and lymph node enlargement, is also considered a risk factor for HGD/IC, albeit with limited evidence [86, 96, 97]. These changes may reflect tumour invasion or obstructive processes.

Cystic Growth Rate

Recent studies have shown that the growth rate of cystic IPMNs is a significant predictor of progression to HGD/IC. A growth rate of ≥2.5 mm/year has been proposed as a WF [98, 99, 100, 101]. This criterion is preferred in current guidelines instead of the previous criterion of ≥5 mm/2 years, which had limited predictive power.

Main Pancreatic Duct Enlargement

While "main pancreatic duct enlargement" may predict aggressive IPMN behaviour, current evidence is insufficient to include it as a WF [4]. Further studies are needed to establish its predictive value.

High-risk stigmata	Worrisome features
1. Mechanical jaundice in patients with cystic changes in the pancreatic head.	1. Acute pancreatitis.
2. Nodule or thickening in the cyst wall ≥ 5 mm or the presence of solid components.	2. Increased serum level of CA19-9.
3. Pancreatic duct diameter ≥ 10 mm.	3. New onset or acute exacerbation of DM within the past year.
4. Suspicious or positive cytology results (if the test was performed)	4. Cyst ≥30 mm.
	5. Enhancing mural nodule < 5 mm.
	6. Thickened/enhancing cyst walls.
	7. MPD ≥ 5 mm and <10 mm.
	8. Abrupt change in calibre of the pancreatic duct with distal pancreatic atrophy.
	9. Lymphadenopathy.
	10. Cystic growth rate ≥2.5 mm/year.

Table 1. The custom table was created based on “International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas [76].”

Additive Risk of Multiple WFs

The impact of multiple WFs on the risk of HGD/IC [104] is additive, gradually increasing with their number. Studies by Zelga et al. show that the risk of HGD/IC increases

stepwise with the number of WFs, reaching 22%, 34%, and 59% for 1, 2, and 3 WFs, respectively, and 100% for patients with four or more WFs [102].

Nomograms for Risk Assessment

Nomograms represent complex statistical patterns that streamline decision-making regarding candidates for surgery or surveillance in IPMN patients [77, 79, 80, 81, 82]. They allow for individual assessment of the risk of HGD/IC based on patient characteristics and WFs. Despite their promising nature, nomograms have limitations, such as the need for more differentiation between different types of IPMNs and the small number of excised IPMNs in some countries. Various factors, including the patient's health condition and preferences, should be considered when utilising nomograms [76].

Worrisome features (WFs) are crucial in identifying IPMNs with a high risk of progression to HGD/IC. Understanding the prognostic significance of WFs, such as acute pancreatitis, elevated CA19-9 levels, and cyst growth rate, is essential for guiding clinical decision-making regarding surgery or surveillance in IPMN patients.

SUMMARY

IPMNs pose formidable diagnostic and therapeutic challenges. However, precise diagnosis, classification, and risk stratification are essential for successful management. This article aims to provide a comprehensive outlook on IPMNs, enabling medical practitioners to adopt a discerning and tailored approach to patients afflicted with this pathology.

The article offers an exhaustive analysis of the diagnostic modalities, classification schemas, and risk assessment methodologies of pancreatic IPMNs, serving as the cornerstone for optimising patient care. With the advent of advanced imaging modalities, pancreatic cysts' detection rate has surged, accentuating the clinical significance of IPMNs. Given their spectrum of benign and malignant potentials, meticulous evaluation is warranted to delineate tailored therapeutic interventions. Despite the intricate nature of this nosological entity, IPMNs furnish invaluable insights into pancreatic neoplasms, enhancing diagnostic accuracy and therapeutic strategies.

This article aims to equip readers with the requisite knowledge base and tools for effective IPMN management. Understanding IPMN diagnosis, classification, and risk stratification is indispensable for optimising clinical outcomes. In addition to providing foundational insights, this article advocates for continued research and clinical refinement in pancreatic oncology.

This article equips readers with the necessary knowledge and tools for effectively managing IPMN. Understanding the diagnosis, classification, and risk stratification of IPMN is essential for optimising clinical outcomes. In addition to providing foundational insights, this article advocates for continuing research and refinement of clinical practice in pancreatic oncology. As we deepen our understanding of IPMN, we can anticipate improvements in patient outcomes, earlier detection of malignant IPMN, and even potential preventive measures.

DISCLOSURE

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