ELMER PRESS

Review

J Curr Surg. 2025;15(1):17-25

Intraductal Papillary Mucinous Neoplasm as a Precursor to Pancreatic Cancer

Sebastian Velastegui-Zurita[a, c], Jordan Llerena-Velastegui[a, b]

Abstract

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a mucin-producing cystic tumor that serves as a significant precursor to pancreatic ductal adenocarcinoma (PDAC). The increasing recognition of IPMN is due to advancements in diagnostic imaging and a deeper understanding of its distinct characteristics. This review aims to consolidate current knowledge on IPMN, focusing on its pathogenesis, epidemiology, clinical manifestations, complications, diagnostic challenges, management, and prognosis. The pathogenesis of IPMN involves genetic mutations such as KRAS, GNAS, and RNF43, which disrupt cellular signaling pathways, leading to mucinous epithelial proliferation and cystic dilation. Epidemiologically, IPMN exhibits varying incidence and prevalence globally, with notable differences based on age, sex, and ethnicity. The clinical presentation of IPMN is often asymptomatic, but when symptoms occur, they are typically nonspecific and can include abdominal pain, weight loss, and new-onset diabetes mellitus. The potential complications of IPMN include pancreatic insufficiency, pancreatitis, and malignant transformation to PDAC. Accurate diagnosis involves a combination of advanced imaging techniques, endoscopic ultrasound, and molecular testing. Management strategies range from monitoring and pharmacological therapy to surgical and non-surgical interventions, with surgical resection recommended for high-risk IPMNs. Despite advancements in therapeutic approaches, gaps remain in understanding the variability of clinical outcomes and the effectiveness of treatment options. Future research should focus on refining diagnostic tools, exploring the molecular and genetic basis of IPMN, and developing targeted therapies to improve early detection and treatment. Enhanced policy support and continued research are essential to improve the management and prognosis of patients with IPMN, ultimately aiming to enhance patient outcomes and inform future therapeutic strategies.

Keywords: Radiology; Treatment; Symptoms; Surgical resection; Genetic mutations

Manuscript submitted June 6, 2024, accepted June 15, 2024
Published online September 16, 2024

[a]Pontifical Catholic University of Ecuador, Medical School, Quito, Ecuador
[b]Center for Health Research in Latin America (CISeAL), Research Center, Quito, Ecuador
[c]Corresponding Author: Sebastian Velastegui-Zurita, Pontifical Catholic University of Ecuador, Medical School, Quito, Ecuador.
Email: sebasvelas123@hotmail.com

doi: https://doi.org/10.14740/jcs479

Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas has garnered significant attention in gastroenterology due to its potential to progress to malignancy. The growing recognition of IPMN is attributed to advancements in diagnostic imaging and a deeper understanding of its unique characteristics. Defined as a mucin-producing cystic tumor, IPMN is categorized within pancreatic diseases as a distinct precursor to pancreatic ductal adenocarcinoma (PDAC). It presents in three primary forms: main duct, branch duct (BD), and mixed type, each with specific implications for pancreatic and extrapancreatic involvement [1].

IPMN is a cystic lesion originating from the ductal epithelium of the pancreas, characterized by mucin-producing cells and the potential to evolve from benign to malignant states. The pathogenesis of IPMN involves mucinous epithelial proliferation and cystic dilation of the pancreatic ducts, driven by genetic mutations such as KRAS, GNAS, and RNF43. These genetic alterations disrupt cellular signaling pathways, leading to the accumulation of mucin and subsequent ductal obstruction, which are key features in the transition from benign lesions to invasive carcinoma [1].

Epidemiologically, IPMN exhibits varying incidence and prevalence globally, influenced by factors such as age, sex, and ethnicity. Studies indicate a higher prevalence of IPMN in males, particularly in Japan and Korea, whereas the distribution is more balanced or female-predominant in the United States and Europe. The typical age of presentation is between the fifth and seventh decades of life. Risk factors include genetic predispositions and lifestyle factors such as smoking and chronic pancreatitis (CP). Additionally, patients with IPMN have a higher incidence of extrapancreatic malignancies, particularly biliary cancer, and a notable association with diabetes mellitus [2].

Clinically, IPMN significantly impacts morbidity and mortality, with main duct involvement posing a higher risk of malignancy. The management of IPMN involves balancing the risk of progression to invasive cancer with the potential for overtreatment. Surgical resection is often recommended for IPMNs with high-risk features such as significant ductal dilation. Recent advancements in therapeutic approaches, including endoscopic and surgical techniques, have shown promise in improving patient outcomes. New therapies, including neoadjuvant chemotherapy and robotic pancreatectomy, offer potential benefits, although further research is needed to establish

optimal treatment strategies [2].

Despite these advancements, gaps remain in understanding the variability of clinical outcomes and the availability of treatment options. There is a need for standardized diagnostic criteria and more effective risk stratification methods to improve the management and prognosis of IPMN. Future research should focus on refining diagnostic tools, exploring the molecular and genetic basis of IPMN, and developing targeted therapies to enhance early detection and treatment [3].

The objective of this review is to provide a comprehensive overview of the current knowledge on the diagnosis, management, and outcomes of IPMN, identifying gaps in the literature and setting directions for future research. By addressing these gaps, we aim to improve the understanding and clinical management of IPMN, ultimately enhancing patient outcomes and informing future therapeutic strategies.

Epidemiology

IPMN of the pancreas was first identified in 1982 when four patients with pancreatic carcinoma and favorable outcomes were reported. These patients exhibited dilated main pancreatic ducts (MPDs), patulous ampullary orifices, and mucus secretion from the pancreatic duct. Since its initial description, the incidence of IPMN has increased, largely attributable to advancements in diagnostic imaging technologies and a better understanding of its distinct characteristics compared to other mucinous cystic neoplasms (MCNs) [4].

The true prevalence of IPMN remains elusive due to the asymptomatic nature of many small lesions. Studies using imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have revealed pancreatic cysts in a notable percentage of patients, many of which are likely IPMNs. Specifically, a series of 2,832 CT scans performed in adults without a history of pancreatic lesions identified pancreatic cysts in 2.6% of cases. In contrast, a study involving 616 patients undergoing MRI found a higher incidence of pancreatic cysts at 13.5%, with a median diameter of 6 mm. IPMNs are estimated to constitute 1-3% of exocrine pancreatic neoplasms and 20-50% of cystic pancreatic neoplasms [5].

The epidemiological data on IPMN show a variation in prevalence based on geographic regions, age groups, and sex. The male-to-female ratio for main duct IPMN ranges from 1.1 to 3:1, whereas for BD IPMN, it ranges from 0.7 to 1.8:1. Geographic differences are notable, with a male predominance observed in Japan and Korea, and a more balanced or female-predominant distribution in the United States and Europe. The typical age of presentation for IPMN is between the fifth and seventh decades of life [6].

Risk factors for IPMN include both genetic and lifestyle components. Genetic predispositions involve specific gene mutations and hereditary cancer syndromes. Notably, mutations in genes such as KLF4, GNAS, KRAS, and RNF43 are frequently associated with IPMNs. Individuals with hereditary pancreatic cancer syndromes, such as those with BRCA1/2 mutations, exhibit a higher prevalence of IPMNs. Additionally, lifestyle factors such as smoking and a history of CP are significant risk factors. Patients with a family history of PDAC, Peutz-Jeghers syndrome, familial adenomatous polyposis syndrome, or familial clustering of pancreatic cancers are also at increased risk [7].

Further complicating the epidemiology of IPMN is its association with other conditions. IPMN patients exhibit a higher prevalence of colorectal cancer and advanced polyps compared to the general population. Diabetes mellitus is present in approximately 25% of IPMN patients, with new-onset or worsening diabetes reported in 6% of cases. Chronic kidney disease also correlates with a higher prevalence of IPMN [6].

In summary, the epidemiology of IPMN highlights the importance of advancements in imaging technology and a deeper understanding of genetic and lifestyle risk factors. These factors contribute to the increased detection and diagnosis of IPMNs, underscoring the need for targeted screening and vigilant monitoring in high-risk populations.

Pathophysiology

IPMN of the pancreas is characterized by the proliferation of mucinous epithelium and cystic dilation of the pancreatic ducts, driven by various biochemical and molecular pathways. The pathophysiology of IPMN begins with the activation of specific genetic mutations that initiate and sustain the disease process [8].

K-ras mutations are identified in approximately half of IPMN cases, playing a crucial role in neoplastic transformation through constitutively active MAP kinase signaling. The tumor suppressor gene CDKN2a is also implicated, along with aberrant expressions of p53 and SMAD4 in a subset of IPMNs. Notably, inactivating mutations in the RNF43 gene and mutations in the GNAS complex locus are frequently observed, with either K-ras or GNAS mutations present in up to 96% of cases. These genetic alterations disrupt cellular signaling pathways, leading to the proliferation and accumulation of mucin-producing cells within the pancreatic ducts [8].

The accumulation of mucin results in ductal obstruction, causing cystic dilation. High-risk stigmata such as dilation of the MPD over 10 mm are significant indicators of malignancy. Advanced imaging techniques, including CT, MRI, and endoscopic ultrasound (EUS), are essential for detecting these changes and guiding clinical management. Surgical resection is often recommended for IPMNs with significant ductal dilation and high-risk features to prevent malignant transformation [6].

Genetic factors play a pivotal role in the progression of IPMN. Specific mutations, including those in KLF4, GNAS, KRAS, RNF43, TP53, SMAD4, and PIK3CA, contribute to the development and advancement of IPMN. These mutations affect cellular signaling and proliferation, with CDX2 expression in intestinal-type IPMNs accelerating the expression of cell cycle markers like p21 and Ki-67. The presence of these mutations highlights the need for genetic surveillance and targeted therapies in managing IPMN [9].

IPMN impacts both the exocrine and endocrine functions of the pancreas. The formation of cysts disrupts the secretion

of digestive enzymes, impairing exocrine function. Endocrine function can also be affected, potentially impacting insulin production and glucose regulation. Accurate diagnosis and detailed reporting of IPMN characteristics, including the highest grade of dysplasia, are crucial for understanding its impact on pancreatic functions and for developing effective management strategies [9].

Recent advancements in therapeutic approaches for IPMN include both surgical and non-surgical methods. Adjuvant chemotherapy has shown to improve overall survival (OS) in node-positive IPMN patients, particularly those with advanced disease and high-risk features. Robotic pancreatectomy offers favorable outcomes, providing a feasible and safe approach for treating IPMN. Non-surgical therapies, such as radiofrequency ablation (RFA) and endoscopic techniques, have emerged as effective alternatives for patients who are not candidates for surgery. RFA, guided by endoscopic techniques, has demonstrated efficacy in reducing lesion size and preventing neoplastic tissue proliferation [9].

In summary, the pathophysiology of IPMN involves a complex interplay of genetic mutations, biochemical pathways, and cellular signaling mechanisms. These factors contribute to mucinous epithelial proliferation, cystic dilation, and pancreatic dysfunction. Advances in diagnostic imaging and therapeutic approaches, including both surgical and non-surgical options, offer promising strategies for managing IPMN and preventing its progression to invasive pancreatic cancer.

Clinical Manifestations

Many patients with IPMN of the pancreas are asymptomatic, with the neoplasm often being detected incidentally during imaging studies performed for unrelated reasons. However, when symptoms do occur, they are typically nonspecific and can include nausea, vomiting, abdominal pain, back pain, weight loss, and anorexia. These symptoms are often subtle and can lead to a delay in diagnosis, sometimes up to several months, due to the insidious nature of the disease and a lack of awareness among clinicians [10].

In some cases, the obstruction of the MPD by mucin can lead to pancreatitis-like symptoms. This obstruction can cause recurrent episodes of abdominal pain, which increase in frequency over time. The presence of mucin-secreting tumors can also result in exocrine and endocrine pancreatic insufficiency, leading to symptoms such as maldigestion and new-onset diabetes mellitus. Diabetes mellitus is particularly significant as it has been associated with an increased risk of MPD involvement, high-grade dysplasia, and invasive cancer. These features highlight the importance of early detection and monitoring of IPMN to prevent progression to more severe forms of the disease [10].

In advanced stages, less common symptoms such as significant weight loss, severe back pain, and worsening diabetes become more prominent. These symptoms are often indicators of a higher risk of malignant transformation. Additionally, rare complications such as peritoneal carcinomatosis and cardiac metastasis can occur, underscoring the aggressive potential of IPMN in its later stages. The presence of these symptoms necessitates close monitoring and potentially more aggressive management to prevent further progression [10].

Pancreatic insufficiency associated with IPMN manifests through symptoms like jaundice, steatorrhea, and weight loss. This insufficiency results from the disruption of both exocrine and endocrine pancreatic functions due to the obstruction and damage caused by mucin-producing neoplasms. Acute pancreatitis is frequently associated with IPMN, particularly in patients with specific epithelial subtypes and higher pancreatic volumes. The production of mucin can obstruct the pancreatic ducts, increasing ductal pressure and inflammation, which can lead to pancreatitis. Patients with IPMN often have a history of preoperative episodes of pancreatitis, suggesting a predisposition to recurrent episodes [11].

IPMN has a significant potential to progress to invasive carcinoma, particularly PDAC. Several factors contribute to this progression, including the presence of diabetes mellitus, high-grade dysplasia, and specific genetic mutations such as KRAS and GNAS. The immune microenvironment also plays a role, with diminished immune surveillance and the presence of immunosuppressive cells facilitating the progression from IPMN to invasive cancer. Clinical and pathological features, such as main duct involvement and larger cyst size, further increase the risk of malignant transformation. Understanding these factors is crucial for stratifying patients for more intensive surveillance and developing targeted therapeutic strategies to prevent the progression of IPMN to invasive cancer [7].

Initial diagnostic tests for IPMN, such as MRI, CT, and EUS, are crucial for identifying and characterizing these neoplasms. MRI with magnetic resonance cholangiopancreatography (MRCP) is particularly recommended for its superior contrast resolution, which helps in detecting intramural nodules, septae, and ductal communication. CT imaging can identify pancreatic steatosis and significant predictors of high-grade dysplasia or malignancy, such as enhanced solid components and a MPD diameter of 10 mm or greater. EUS, often combined with fine-needle aspiration (FNA), is effective in identifying mucinous cystic lesions and assessing malignancy risk. These diagnostic tools, when used in combination, provide a comprehensive approach to diagnosing and managing IPMN, allowing for accurate characterization and appropriate therapeutic planning [8].

Complications

IPMN of the pancreas can lead to several significant complications, each of which impacts patient outcomes and requires specific management strategies. One of the most common complications is pancreatic insufficiency, resulting from the obstruction and damage caused by mucin-producing neoplasms. This insufficiency manifests in both exocrine and endocrine forms, leading to symptoms such as malnutrition, weight loss, steatorrhea, and diabetes mellitus. The risk of pancreatic insufficiency is notably higher in patients with a history of pancreatitis and in those with specific epithelial subtypes. Effective management involves pancreatic enzyme replace-

ment therapy (PERT) to alleviate malnutrition and improve the quality of life. PERT has demonstrated survival benefits and is essential for managing symptoms related to pancreatic insufficiency [10].

IPMN is also associated with the development of pancreatitis. The mucin production by the neoplasm can obstruct pancreatic ducts, causing increased ductal pressure and inflammation. This often results in acute pancreatitis, particularly in patients with intestinal and pancreatobiliary subtypes, which are more prone to these complications. Therapeutic approaches for managing pancreatitis in IPMN patients range from medical management to endoscopic and surgical interventions. Surgical resection is frequently recommended for high-risk IPMNs to prevent further complications and malignant transformation. Advanced endoscopic techniques, such as EUS with FNA, are instrumental in diagnosing and stratifying risk, thereby guiding appropriate intervention [10].

A significant concern with IPMN is its potential for malignant transformation. The progression to invasive carcinoma, specifically PDAC, involves multiple genetic and molecular mechanisms. Mutations in genes such as KRAS, GNAS, and RNF43 are frequently observed in IPMN and are critical in the transition from non-invasive to invasive stages. Additional mutations in SMAD4 and TGFBR2 are often restricted to invasive carcinomas, indicating their role in driving invasion. The transition from low-grade to high-grade dysplasia involves significant changes in gene expression, immune microenvironment alterations, and increased tumor stemness. These factors highlight the need for early detection and intervention strategies to prevent malignant progression [5].

Post-surgical complications are also a concern following the resection of IPMN. Risk factors for complications include elevated levels of carbohydrate antigen 19-9 (CA19-9), larger tumor size, and specific pathological features such as lymph node metastasis and malignant margins. These factors are associated with higher recurrence rates and poorer disease-specific survival. The prevalence of post-surgical complications, such as infections and pancreatic fistula formation, is relatively high, with reported rates around 20%. Prevention strategies include advanced surgical techniques, such as end-to-end anastomosis reconstruction with stent placement, proper risk stratification, and regular monitoring. These approaches aim to minimize the risk of postoperative complications and improve patient outcomes [6].

In conclusion, the complications associated with IPMN of the pancreas are multifaceted, involving pancreatic insufficiency, pancreatitis, malignant transformation, and post-surgical issues. Effective management and prevention strategies are essential to improve patient outcomes and prevent the progression of IPMN to more severe forms of disease. Understanding the genetic and molecular mechanisms underlying these complications is crucial for developing targeted therapies and optimizing patient care.

Diagnostic Criteria and Challenges

IPMN of the pancreas presents unique diagnostic challenges due to its variable clinical manifestations and potential for malignant transformation. Early suspicion of IPMN should arise from a combination of clinical indicators, such as nonspecific abdominal pain, weight loss, jaundice, and new-onset diabetes mellitus, especially in patients with risk factors like a family history of pancreatic diseases. Laboratory markers, including elevated CA19-9 and carcinoembryonic antigen (CEA) levels, although not definitive, can raise suspicion when correlated with imaging findings [7].

The systematic diagnostic approach for IPMN begins with comprehensive clinical assessment and detailed family history, emphasizing any hereditary predispositions. Cross-sectional imaging, primarily using MRI/MRCP or CT, is typically the first step. These imaging modalities are critical in identifying key features of IPMN, such as cystic lesions, ductal dilatation, and the presence of mural nodules. MRI/MRCP is particularly advantageous due to its superior contrast resolution, which helps in differentiating mucinous from non-mucinous cysts and in visualizing the internal architecture of the pancreatic ducts [8].

EUS with FNA is often employed for further evaluation when initial imaging suggests malignancy or when high-risk features are present, such as a MPD diameter greater than 10 mm, enhancing solid components, or associated obstructive jaundice. EUS provides high-resolution imaging and the opportunity to obtain cytological samples and cyst fluid for analysis, enhancing the diagnostic precision. Specific EUS findings indicative of malignancy include large mural nodules, irregular cystic structures, and ductal abnormalities [9].

Cytological examination of aspirated cyst fluid can reveal atypical or malignant cells, though its sensitivity is limited by the high rate of nondiagnostic samples. The analysis of cyst fluid for biomarkers, such as elevated CEA levels, can assist in differentiating mucinous from non-mucinous cysts. Molecular testing for mutations in genes like KRAS, GNAS, and P53, as well as assessing telomerase activity, provides additional insights into the malignant potential of IPMNs [10].

Advanced imaging techniques, such as diffusion-weighted MRI (DW-MRI), further refine the diagnostic process by differentiating benign from malignant lesions based on apparent diffusion coefficient (ADC) values. Radiomic analysis of multiphase CT scans also enhances the prediction of malignancy, particularly when integrated with conventional imaging criteria [1].

Biomarker analysis plays an increasingly significant role in the diagnosis and risk stratification of IPMN. Elevated levels of circulating cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2R, IL-6, and IL-8, have been associated with malignant IPMNs. Gene expression profiles, including upregulated and downregulated genes identified through molecular testing, provide crucial information on the progression risk of IPMN. The presence of specific genetic mutations, such as those in the GNAS and KRAS genes, further aids in assessing malignancy risk [12].

In summary, the diagnosis of IPMN involves a multifaceted approach combining clinical evaluation, advanced imaging, EUS-FNA, and molecular testing. These methods collectively improve the accuracy of diagnosis, enable precise risk stratifi-

cation, and guide appropriate clinical management to prevent progression to invasive pancreatic cancer.

Differential Diagnosis

IPMN is a type of pancreatic cystic lesion that can potentially transform into PDAC. Differentiating IPMN from other pancreatic cystic lesions such as MCN and serous cystadenoma (SCA) is crucial for appropriate clinical management due to their distinct biological behaviors and treatment strategies [13].

The differentiation of IPMN from other pancreatic cystic lesions can be effectively achieved using specific imaging patterns. Central scarring, central calcification, and the circumvascular sign on CT are key features for identifying SCAs. Additionally, 68Ga- fibroblast-activation protein inhibitor (FAPI) positron emission tomography (PET) imaging is a promising tool for distinguishing between benign and malignant IPMN, aiding in the appropriate clinical management of these lesions. Central scarring and central calcification are specific CT features that help distinguish SCAs from MCNs and BD IPMNs. These features, when combined with the circumvascular sign, significantly increase diagnostic sensitivity for SCAs. The circumvascular sign on CT is a specific feature for diagnosing SCAs and differentiating them from MCNs and BD IPMNs. This sign, when combined with either central scarring or central calcification, enhances diagnostic accuracy. 68Ga-FAPI PET imaging shows significantly elevated uptake in menacing (high-grade) IPMN compared to low-grade IPMN and other benign cystic lesions. This imaging modality provides high sensitivity and specificity for differentiating between benign and malignant IPMN, potentially avoiding unnecessary surgeries [13].

CP and IPMN are two distinct pancreatic conditions that can present with overlapping clinical and imaging features. Differentiating between these conditions is crucial for appropriate management and prognosis. IPMN often presents with a dilated MPD and large cystic lesions, whereas CP typically shows irregular ductal dilatation without such large cystic formations. Calcifications are more commonly associated with CP. In contrast, IPMN may show calcifications within cystic lesions but not as a predominant feature. IPMN is characterized by the presence of mural nodules within cystic lesions or the MPD, and sometimes a fistula to adjacent organs. CP often shows strictures and irregularities in the ductal system without these specific features. Decreased CT number in the pancreatic parenchyma is a reliable imaging biomarker for malignancies in IPMN patients, indicating high-risk stigmata. This feature is not typically seen in CP. DW-MRI metrics can differentiate between benign IPMN and invasive pancreatic cancer, with IPMN showing higher ADC values compared to pancreatic cancer. CP does not exhibit these specific DW-MRI characteristics. 68Ga-FAPI PET imaging shows elevated uptake in menacing IPMN compared to low-grade IPMN and other benign cystic lesions, providing a tool for differentiation. This imaging modality is not typically used for CP. Differentiating CP from IPMN involves a combination of imaging features and clinical presentations. IPMN is often associated with a significantly dilated MPD, large cystic lesions, and specific features such as mural nodules and fistulas. Calcifications are more indicative of CP. Advanced imaging techniques like DW-MRI and 68Ga-FAPI PET can further aid in distinguishing these conditions, with IPMN showing distinct imaging biomarkers and uptake patterns [13].

IPMN and PDAC are two distinct entities within pancreatic pathology. Differentiating between these conditions is crucial for appropriate clinical management. Menacing IPMN shows significantly elevated 68Ga-FAPI uptake compared to low-grade IPMN and other benign cystic lesions. Dynamic imaging reveals distinct time-activity curves for menacing versus low-grade IPMN. Colloid carcinoma (a type of IPMN) is associated with larger MPD size, larger cystic lesion diameter, septation, calcification, mural nodules, and fistula presence. Tubular adenocarcinoma (PDAC) is associated with extracystic or extraductal solid masses and abrupt changes in MPD caliber. IPMN lesions show higher ADC values compared to PDAC, indicating differences in tumor cell density and architecture. Cytomorphological features on FNA specimens, histopathological correlation, and immunohistochemical markers such as CPA1, CPA2, and GP2 are useful in distinguishing acinar cell neoplasms from other pancreatic tumors, including IPMN and PDAC. Tumor marker profiles, such as CA19-9, may also differ between the two conditions. The presence of IPMN in patients with PDAC is an independent predictive factor for the development of new PDAC in the remnant pancreas after partial pancreatectomy [14].

Pancreatic neuroendocrine tumors (pNETs) are a diverse group of neoplasms originating from the endocrine tissues of the pancreas. Diagnosing these tumors involves a combination of biochemical markers, imaging techniques, and histopathological analysis. Chromogranin A and synaptophysin are the most specific immunohistochemical markers for pNETs, with nearly 100% of pNETs being positive for both markers. Insulinoma-associated protein 1 (INSM1) is a robust marker for identifying and grading pNETs. S100 protein and neuronal specific enolase (NSE) are also useful in diagnosing pNETs. Somatostatin receptor PET/CT (SSR-PET/CT) is highly effective for detecting primary lesions and initial staging of pNETs, particularly for well-differentiated tumors. 68Ga-DOTA-peptide PET/CT is recommended for staging and restaging of non-insulinoma well-differentiated pNETs, and for evaluating *in vivo* somatostatin receptor expression to select candidates for peptide receptor radiometabolic treatment. Emerging biomarkers such as circulating tumor cells, multiple transcript analysis, microRNA profiles, and cytokines require further investigation before clinical application. NETest liquid biopsy and circulating microRNAs are gaining importance in molecular identification and diagnostics. Immunohistochemical examination is essential for confirming the neuroendocrine nature of the tumor and determining the potential malignancy using markers like Ki-67, p53, and AMACR. Proper handling of tissue samples is crucial for reliable diagnosis [14].

Solid pseudopapillary neoplasms (SPNs) and IPMNs are two distinct types of pancreatic tumors. Understanding their differences in demographics, imaging, and histopathologi-

cal features is crucial for accurate diagnosis and treatment. SPNs typically affect younger women, often in their second to fourth decades of life, whereas IPMNs are more common in older adults, with a higher prevalence in men. SPNs usually appear as a well-circumscribed, encapsulated mass with both solid and cystic components on imaging studies. IPMNs are characterized by cystic lesions that communicate with the pancreatic ductal system, often showing dilation of the MPD or its branches. Histopathologically, SPNs show a combination of solid and pseudopapillary patterns with uniform cells and occasional nuclear grooves. They often have hemorrhagic and cystic degeneration. IPMNs exhibit papillary growth within the pancreatic ducts, with mucin production and varying degrees of dysplasia, and can progress to invasive carcinoma. These differences in demographic profiles, imaging characteristics, and histopathological features aid in the differential diagnosis of these pancreatic neoplasms [8].

Management and Treatment

The management and treatment of IPMN of the pancreas involve various strategies, ranging from monitoring and pharmacological therapy to surgical and non-surgical interventions, as well as advanced management options. Accurate evaluation and monitoring are crucial for determining the appropriate treatment strategy, including surgical intervention or surveillance. Several protocols and technologies have been developed to track the progression of IPMNs [15].

High-resolution imaging techniques and EUS are essential for evaluating IPMNs to identify patients who need surgical treatment or surveillance. A deep learning protocol using convolutional neural networks (CNNs) applied to MRI can classify IPMNs with sensitivity and specificity comparable to current radiographic criteria. Additionally, EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) combined with CNN-based computer-aided diagnosis (CAD) algorithms can differentiate high-grade dysplasia/adenocarcinoma in IPMNs with higher sensitivity and accuracy compared to traditional guidelines. Tracking the progression of IPMNs involves a combination of high-resolution imaging techniques, EUS, and advanced AI-driven protocols. These methods offer accurate and sensitive tools for diagnosing and risk stratifying IPMNs, potentially improving patient outcomes through better-informed treatment decisions [15].

Pharmacological therapy plays a significant role in managing IPMN symptoms and progression. Adjuvant chemotherapy can improve disease-specific survival (DSS) in patients with invasive IPMN, particularly those with nodal disease or tubular differentiation. Surgical excision remains the primary treatment for IPMN, with the method of surgery varying based on the lesion's location. For main-duct IPMNs with significant malignancy risk, surgical intervention is often necessary. The use of EUS, endoscopic retrograde cholangiopancreatography (ERCP), and direct visualization systems can help achieve precise treatment of IPMN. The management of IPMN symptoms primarily involves surgical excision, especially for main duct IPMNs with significant malignancy risk. Advanced endoscopic techniques can aid in the precise treatment of IPMN. Further research, particularly randomized controlled trials, is needed to refine these treatment strategies [6].

Surgical interventions for IPMN vary based on the type and extent of the disease. Main duct and mixed type IPMNs generally require surgical resection, while small, asymptomatic BD IPMNs can be monitored. Partial pancreatectomy is effective for non-invasive cases, while total pancreatectomy is reserved for more extensive disease. Adjuvant therapy, including chemotherapy and radiotherapy, is beneficial for patients with node-positive disease, higher TNM stage, positive resection margins, poor differentiation, and tubular subtype. Surgical intervention for IPMN varies based on the type and extent of the disease. Partial pancreatectomy is effective for non-invasive cases, while total pancreatectomy is reserved for more extensive disease. Adjuvant therapy is beneficial in specific invasive cases, particularly those with nodal involvement or poor differentiation [14].

Non-surgical interventions, particularly endoscopic therapies, play a crucial role in the management of IPMNs, offering advanced diagnostic capabilities and minimally invasive therapeutic options. EUS and ERCP are pivotal in early detection, risk stratification, and precise treatment of IPMNs. Innovative endoscopic techniques continue to improve the accuracy and effectiveness of IPMN management, providing alternatives to more invasive surgical procedures. Lifestyle modifications, while not extensively documented, are considered beneficial in managing IPMN based on risk stratification and the progression of the disease [8].

Advanced management options include novel endoscopic techniques and emerging therapies. Techniques such as EUS-guided FNA, advanced imaging and biopsy methods, EUS-guided ablation, and photodynamic therapy are enhancing the diagnosis and treatment of IPMNs. These advancements offer promising alternatives to traditional surgical methods, potentially improving patient outcomes through more accurate and less invasive approaches. Emerging therapies for IPMNs, particularly adjuvant chemotherapy, show promise in improving survival rates for specific subtypes of invasive IPMNs, such as those with nodal involvement or tubular differentiation. Further clinical trials are necessary to solidify these findings and optimize treatment protocols [9].

Prognosis

The prognosis of IPMN is influenced by various clinical, radiological, and biochemical factors. Risk factors for malignancy in IPMN include symptoms, cyst size equal to or greater than 3 cm, cyst wall thickening, mural nodules, MPD dilatation, abrupt caliber change of the pancreatic duct, lymphadenopathy, elevated CA19-9, and elevated CEA levels. Diabetes mellitus is also associated with a higher risk of MPD involvement, high-grade dysplasia, and invasive cancer in IPMN patients. Predictive models and biomarkers are essential tools in stratifying the malignancy risk. A random forest model identified mural nodule size, MPD diameter, CA19-9 levels, lesion edge, and common bile duct dilation as key factors for predicting

malignancy in IPMNs. Circulating cytokines such as TNF-α, IL-2R, IL-6, and IL-8 can help identify malignant IPMNs. Molecular phenotyping, including mutations in KRAS and GNAS, and protein expressions of p16, p53, SMAD4, and STK11, can stratify the risk of invasion and survival in IPMN patients [16].

Mural nodule size and obstructive jaundice are significant pre-operative prognostic markers for disease-specific survival and recurrence-free survival in IPMN patients. Lower prognostic nutritional index (PNI) and elevated CA19-9 levels are significant predictors of lymph node metastasis in IPMN patients. Concomitant IPMN in patients with PDAC is an independent predictive factor for the development of new PDAC in the remnant pancreas [15].

Various tools and methods are available to assess the prognosis and malignant potential of IPMNs. Diffusion-weighted imaging (DWI) is effective in differentiating between benign and malignant IPMNs, with high sensitivity and specificity. Nomograms based on clinical and pathological factors provide improved predictive accuracy for OS and cancer-specific survival compared to traditional staging systems. PET with 18-FDG is more sensitive, specific, and accurate than standard imaging criteria in detecting malignant IPMNs, making it a valuable tool for managing patients with uncertain imaging findings. A CT-based nomogram incorporating features like enhancing mural nodule size, MPD diameter, abrupt change in MPD caliber with distal pancreatic atrophy, cyst size, thickened enhancing cyst wall, and lymphadenopathy can preoperatively predict high-risk IPMNs with high accuracy [16].

Patients with IPMNs generally have favorable survival rates, especially when the disease is non-invasive. The 5-year OS and disease-free survival (DFS) rates for IPMNs are 97.5% and 80.6%, respectively. Patients with invasive IPMNs have a worse 5-year survival rate of 48.4% compared to those with low-grade dysplasia (89.0%) or high-grade dysplasia (84.0%). Adjuvant chemotherapy significantly improves OS in patients with node-positive invasive IPMNs, reducing the risk of death and extending median survival. The 5-year recurrence-free survival rate for resectable invasive IPMNs is 61%, with key risk factors for recurrence including CA19-9 levels equal to or greater than 83 U/mL, tumor size equal to or greater than 2.2 cm, and lymph node metastasis [16].

Quality of life measures associated with IPMN are closely linked to accurate diagnosis and effective prediction of malignancy. High-risk stigmata such as MPD dilation, mural nodules, and obstructive jaundice are strongly associated with malignant IPMN. Nomograms based on comprehensive clinical and non-invasive examination variables offer superior predictive accuracy and clinical utility, aiding in better risk classification and treatment planning for patients with IPMN [16].

Common complications associated with IPMNs include a high prevalence of diabetes mellitus, which is linked to an increased risk of malignancy, and a significant incidence of extrapancreatic malignancies, particularly biliary cancer. The presence of multiple worrisome features or high-risk stigmata significantly elevates the risk of malignancy. Additionally, rare but severe complications such as fistula formation into adjacent organs can occur, underscoring the need for vigilant monitoring and management of IPMN patients [17].

Gaps in the Literature

In the study of IPMN, several areas lack sufficient data, particularly regarding long-term treatment effects and early diagnostic indicators. One significant research gap is the prevalence and risk factors of diabetes mellitus in IPMN patients. Diabetes mellitus is prevalent in 25% of IPMN patients and is associated with a higher risk of MPD involvement, high-grade dysplasia, and invasive cancer. The diagnostic value of the MPD diameter is also crucial, with MPD dilatation of ≥ 5 mm being a significant indicator of malignancy in IPMN. This marker has higher sensitivity and odds ratios for detecting high-grade dysplasia and invasive carcinoma compared to a ≥ 10 mm cutoff [18].

Current guidelines for IPMN management reveal variations in diagnostic accuracy and treatment recommendations. The 2018 European guidelines are more aggressive, suggesting resection for any patient with moderate-risk features, resulting in higher sensitivity but lower specificity compared to the 2017 International guidelines. EUS can improve diagnostic accuracy for patients with moderate-risk features [19].

Insufficient data exist in several key areas of IPMN research. Long-term surveillance of BD IPMN without high-risk features is limited. Accurate diagnosis of advanced neoplasia in IPMN is challenging, necessitating further research to improve diagnostic accuracy and clinical management. The relationship between IPMN and pancreatic cancer, as well as the mechanism of progression from IPMN to invasive carcinoma, requires further exploration. Additionally, the clinicopathological features of IPMN derived from ectopic pancreas are not well understood, highlighting the need for more comprehensive data in this area [18].

In summary, the study of IPMN reveals several areas with insufficient data, particularly in understanding the long-term effects of treatment and early diagnostic indicators. Diabetes mellitus is a significant risk factor for more aggressive IPMN, and MPD dilatation is a critical diagnostic marker. Current guidelines vary in their approach, with European guidelines being more aggressive but less specific. Further research is needed to refine these guidelines and improve early diagnostic tools.

Future Directions

The study of IPMNs reveals several promising directions for future research. Current diagnostic methods are inadequate, emphasizing the necessity for identifying efficient biomarkers and targeted therapeutic approaches to improve early diagnosis and risk stratification. Gene expression and biomarker studies have highlighted a range of genetic and molecular markers with potential clinical application. For instance, meta-analyses have identified numerous upregulated and downregulated genes in high-risk IPMNs, suggesting these could serve as biomarkers for high-risk cases. Additionally, the detection of specific autoreactive antibodies in the blood offers a promising method for distinguishing between different grades of IPMN dysplasia and early-stage PDAC. Similarly, reduced levels of apolipoprotein A2-isoforms in IPMN samples have shown high diagnostic performance for detecting high-grade dysplasia and IPMN-associ-

ated carcinoma [20].

Micro-RNAs (miRNAs) and long noncoding RNAs (lncRNAs) have also emerged as crucial elements in the diagnostic landscape of IPMN. Certain miRNAs, significantly enriched in IPMN carcinoma compared to adenoma, have been identified as potential diagnostic markers for malignant transformation. Additionally, the identification of various miRNAs and lncRNAs and their target genes provides valuable insights into the regulatory mechanisms during IPMN progression [20].

The assessment of circulating cytokines, such as TNF-α, IL-2R, IL-6, and IL-8, proposes novel predictive models to improve diagnostic accuracy for malignant IPMNs. These cytokines offer a promising avenue for future research, with potential implications for developing targeted therapeutic strategies [16].

Future research should also focus on the genetic characteristics of IPMN and their relationship to pancreatic cancer. The identification of clinically relevant genetic biomarkers with high mutation rates necessitates further investigation to improve IPMN stratification and risk assessment. Large-scale and independent cohort studies are essential to validate these findings and translate them into clinical practice [17].

Moreover, the integration of advanced imaging tools and innovative diagnostic techniques, such as through-the-needle microforceps biopsy and nCLE, holds promise for enhancing diagnostic accuracy and clinical management of IPMN. Further research into these interventional techniques is needed to establish their utility in routine clinical practice [18].

In conclusion, future directions in the study of IPMNs should prioritize the validation and clinical application of identified biomarkers, the exploration of genetic and molecular markers, and the advancement of diagnostic and therapeutic techniques. These efforts are crucial for improving early diagnosis, risk stratification, and the overall management of IPMN, ultimately enhancing patient outcomes.

Conclusion

In conclusion, the comprehensive review of IPMN of the pancreas underscores several critical insights and implications for clinical practice. IPMN is recognized as a significant precursor to PDAC, necessitating early and accurate diagnosis to prevent malignant progression. The pathogenesis of IPMN involves complex genetic mutations, including KRAS, GNAS, and RNF43, which disrupt cellular signaling pathways and contribute to mucinous epithelial proliferation and cystic dilation. The epidemiological data reveal variations in incidence and prevalence based on age, sex, and geographic regions, highlighting the need for targeted screening and vigilant monitoring, especially in high-risk populations. Clinically, IPMN impacts morbidity and mortality, with main duct involvement posing a higher risk of malignancy. Management strategies must balance the risk of progression to invasive cancer with the potential for overtreatment, with surgical resection recommended for high-risk IPMNs. Recent advancements in therapeutic approaches, including endoscopic and surgical techniques, show promise in improving patient outcomes. However, significant gaps remain in understanding the variability of clinical outcomes and the availability of treatment options. Future research should focus on refining diagnostic tools, exploring the molecular and genetic basis of IPMN, and developing targeted therapies to enhance early detection and treatment. Continued research and enhanced policy support are essential to improve the management and prognosis of patients with IPMN, ultimately aiming to enhance patient outcomes and inform future therapeutic strategies.

Learning Points

IPMN is a significant precursor to PDAC, necessitating early and accurate diagnosis.

Genetic mutations such as KRAS, GNAS, and RNF43 play crucial roles in IPMN pathogenesis, leading to mucinous epithelial proliferation and cystic dilation.

Clinical manifestations are often asymptomatic but can include nonspecific symptoms like abdominal pain, weight loss, and new-onset diabetes mellitus.

Accurate diagnosis requires a combination of advanced imaging techniques, EUS, and molecular testing.

Management strategies include monitoring, surgical resection for high-risk IPMNs, and exploring targeted therapies to improve early detection and treatment.

Acknowledgments

The authors have no acknowledgements to declare, reflecting the independent completion of the work.

Financial Disclosure

No funding was received for the conduct of this study or the preparation of this article, indicating that there are no financial sources to declare.

Conflict of Interest

The authors declare no conflict of interest to ensure the impartiality of the review.

Author Contributions

Sebastian Velastegui-Zurita, MD: conceptualization, supervision, project administration, writing - review and editing; Jordan Llerena-Velastegui, MD: formal analysis, data curation, writing - review and editing.

Data Availability

All data generated or analyzed during this study are included in this published article, and further inquiries should be directed to the corresponding author.

References

1. Triantopoulou C, Gourtsoyianni S, Karakaxas D, Delis S. Intraductal papillary mucinous neoplasm of the pancreas: a challenging diagnosis. Diagnostics (Basel). 2023;13(12):2015. doi pubmed pmc
2. Wu RS, Liao WJ, Ma JS, Wang JK, Wu LQ, Hou P. Epidemiology and outcome of individuals with intraductal papillary neoplasms of the bile duct. World J Gastrointest Oncol. 2023;15(5):843-858. doi pubmed pmc
3. Pavlidis ET, Sapalidis KG, Pavlidis TE. Modern aspects of the management of pancreatic intraductal papillary mucinous neoplasms: a narrative review. Rom J Morphol Embryol. 2022;63(3):491-502. doi pubmed pmc
4. Takahashi H, Adachi Y, Nakahara K, Kikuchi T, Mita H, Nakamura M, Yoshida Y, et al. Intraductal Papillary Mucinous Neoplasm with Pancreatogastric Fistula. Intern Med. 2021;60(8):1211-1215. doi pubmed pmc
5. Grutzmann R, Post S, Saeger HD, Niedergethmann M. Intraductal papillary mucinous neoplasia (IPMN) of the pancreas: its diagnosis, treatment, and prognosis. Dtsch Arztebl Int. 2011;108(46):788-794. doi pubmed pmc
6. Machado NO, Al Qadhi H, Al Wahibi K. Intraductal papillary mucinous neoplasm of pancreas. N Am J Med Sci. 2015;7(5):160-175. doi pubmed pmc
7. Lee JH, Kim Y, Choi JW, Kim YS. KRAS, GNAS, and RNF43 mutations in intraductal papillary mucinous neoplasm of the pancreas: a meta-analysis. Springerplus. 2016;5(1):1172. doi pubmed pmc
8. Mas L, Lupinacci RM, Cros J, Bachet JB, Coulet F, Svrcek M. Intraductal papillary mucinous carcinoma versus conventional pancreatic ductal adenocarcinoma: a comprehensive review of clinical-pathological features, outcomes, and molecular insights. Int J Mol Sci. 2021;22(13):6756. doi pubmed pmc
9. Hu Y, Jones D, Esnakula AK, Krishna SG, Chen W. Molecular pathology of pancreatic cystic lesions with a focus on malignant progression. Cancers (Basel). 2024;16(6):1183. doi pubmed pmc
10. Shi C, Hruban RH. Intraductal papillary mucinous neoplasm. Hum Pathol. 2012;43(1):1-16. doi pubmed
11. Zhang C, Al-Shaheri FN, Alhamdani MSS, Bauer AS, Hoheisel JD, Schenk M, Hinz U, et al. Blood-Based Diagnosis and Risk Stratification of Patients with Pancreatic Intraductal Papillary Mucinous Neoplasm (IPMN). Clin Cancer Res. 2023;29(8):1535-1545. doi pubmed pmc
12. Paramythiotis D, Karlafti E, Fotiadou G, Charalampidou M, Karakatsanis A, Ioannidis A, Michalopoulos A. Pancreatic Intraductal Papillary Mucinous Neoplasms: A Narrative Review. Acta Med Litu. 2023;30(1):53-65. doi pubmed pmc
13. Lang M, Spektor AM, Hielscher T, Hoppner J, Glatting FM, Bicu F, Hackert T, et al. Static and dynamic (68)Ga-FAPI PET/CT for the detection of malignant transformation of intraductal papillary mucinous neoplasia of the pancreas. J Nucl Med. 2023;64(2):244-251. doi pubmed pmc
14. Dumlu EG, Karakoc D, Ozdemir A. Intraductal papillary mucinous neoplasm of the pancreas: current perspectives. Int Surg. 2015;100(6):1060-1068. doi pubmed pmc
15. Pu N, Chen Q, Zhang J, Yin H, Wang D, Ji Y, Rao S, et al. Circulating cytokines allow for identification of malignant intraductal papillary mucinous neoplasms of the pancreas. Cancer Med. 2023;12(4):3919-3930. doi pubmed pmc
16. Wu YHA, Oba A, Beaty L, Colborn KL, Rodriguez Franco S, Harnke B, Meguid C, et al. Ductal dilatation of >/=5 mm in intraductal papillary mucinous neoplasm should trigger the consideration for pancreatectomy: a meta-analysis and systematic review of resected cases. Cancers (Basel). 2021;13(9):2031. doi pubmed pmc
17. Huang X, Guo T, Zhang Z, Cai M, Guo X, Zhang J, Yu Y. Prediction of malignant intraductal papillary mucinous neoplasm: A nomogram based on clinical information and radiological outcomes. Cancer Med. 2023;12(16):16958-16971. doi pubmed pmc
18. Pollini T, Wong P, Maker AV. The landmark series: intraductal papillary mucinous neoplasms of the pancreas-from prevalence to early cancer detection. Ann Surg Oncol. 2023;30(3):1453-1462. doi pubmed pmc
19. Crippa S, Arcidiacono PG, De Cobelli F, Falconi M. Review of the diagnosis and management of intraductal papillary mucinous neoplasms. United European Gastroenterol J. 2020;8(3):249-255. doi pubmed pmc
20. Saha B, Chhatriya B, Pramanick S, Goswami S. Bioinformatic analysis and integration of transcriptome and proteome results identify key coding and noncoding genes predicting malignancy in intraductal papillary mucinous neoplasms of the pancreas. Biomed Res Int. 2021;2021:1056622. doi pubmed pmc