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REVIEW ARTICLE

Diagnosis and Management of Intraductal Papillary Mucinous Neoplasms: Focusing on Precancerous Lesions

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Pancreatic intraductal papillary mucinous neoplasms (IPMNs) are precancerous lesions with variable malignant potential, highlighting the importance of accurate diagnostic and treatment strategies. This review summarizes recent advancements in epidemiologic understanding, molecular pathogenesis, and international/society guidelines regarding IPMN management. The rising global incidence of IPMN, driven by aging populations and increased imaging, underscores the growing clinical significance of these tumors. Main-duct and mixed-type subtypes exhibit much higher malignant transformation rates (approximately 59%) than branch-duct IPMN (approximately 8%). Molecular analyses identified early dual *KRAS* and *GNAS* mutations as key drivers of IPMN, with subsequent *RNF43*, *TP53*, and *SMAD4* mutations associated with its progression to invasive carcinoma. Diagnostic accuracy has improved with cyst fluid next-generation sequencing, demonstrating high sensitivity and specificity. International/society guidelines, such as Fukuoka guidelines, American Gastroenterological Association guidelines, European evidence-based guidelines on pancreatic cystic neoplasms, and the 2024 Kyoto guidelines, differ significantly regarding surgical indications and surveillance strategies. Notably, Kyoto guidelines incorporate molecular markers into risk assessment and suggest the discontinuation of surveillance for small (≤ 2 cm) branch-duct IPMNs that remain stable for 5 years. Innovations, such as artificial intelligence-driven radiomics, have rendered malignant transformation more predictable. However, standardizing these technologies and addressing cost-effectiveness remain challenging. Future research directions include validating integrated diagnostic models, refining surveillance intervals based on precise risk stratification, and exploring novel molecular and immune markers. Ultimately, adopting a comprehensive, personalized management approach for IPMN is critical to minimizing overtreatment, preventing invasive pancreatic cancer, and optimizing patient outcomes.

Key Words: Pancreatic cyst; Pancreatic intraductal neoplasms; Cell transformation, neoplastic; Pancreatic neoplasms; Biomarkers, tumor

INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies globally, with a poor prognosis and rapidly rising incidence, both domestically and internationally [1]. In the United States, pancreatic cancer is projected to become the second leading cause of cancer-related death by 2030, surpassing colorectal cancer [2]. In South Korea, pancreatic cancer surpassed gastric cancer for the first time in 2022, becoming the fourth leading cause of cancer-related mortality [3]. According to the Korea National Cancer Registry statistics from 2021, the 5-year relative survival rate for pancreatic cancer remains low, at approximately 15.9%, highlighting the critical need for improved diagnostic strategies and early intervention [4]. Pancreatic cancer is currently the seventh leading cause of cancer mortality worldwide and is predicted to rise to the second or third leading cause in some Western countries by 2030, mainly because of aging populations and

ongoing diagnostic challenges.

In contrast, intraductal papillary mucinous neoplasms (IPMNs) of the pancreas represent precancerous lesions that are more amenable to early detection and preventive intervention. Approximately 10% of all pancreatic cancers are estimated to arise from IPMN, underscoring the significance of IPMN as a potential therapeutic target for early management and cancer prevention [5,6].

IPMNs are anatomically and histologically classified into main-duct (MD), branch-duct (BD), and mixed-type (MT) subtypes and pathologically graded as low-grade dysplasia, high-grade dysplasia, or invasive carcinoma [7]. A recent meta-analysis found that MD-IPMNs and MT-IPMNs have a high likelihood of malignant transformation, with 59% (95% confidence interval, 54–64%) demonstrating high-grade dysplasia or invasive carcinoma at the time of surgical resection. Conversely, the malignant transformation rate for BD-IPMNs was only 8.2% after long-term follow-up exceeding 10 years [8]. This notable difference in malignancy risk between subtypes highlights the need for individualized risk assessment and management plans.

Molecular studies have revealed that IPMN most commonly harbors dual *KRAS* and *GNAS* mutations. Further progression to high-grade dysplasia or invasive carcinoma involves the accumulation of additional genetic alterations [9]. Liquid biopsy methods, such as circulating cell-free DNA (cfDNA) analysis and next-generation sequencing (NGS) of cyst fluid, have demonstrated promising diagnostic accuracy, with high specificity and moderate-to-high sensitivity for detecting at least one *KRAS* or *GNAS* mutation [10]. These molecular markers, combined with imaging and clinical indicators, are currently being refined into precise prognostic tools for improved patient management.

Clinical guidelines for IPMN management have been revised frequently over the past 2 decades. The Sendai guidelines in 2006 and the subsequent Fukuoka guidelines in 2012 and 2017 introduced the concepts of high-risk stigmata (HRS) and worrisome features (WF) to stratify indications for surgery [11]. However, concerns have been raised about the low specificity of these guidelines, potentially leading to unnecessary surgical resections. The 2018 European evidence-based guidelines further refined indications for surgery by introducing relative and absolute criteria and including elevated carbohydrate antigen (CA) 19-9 levels as a consideration for surgery [12]. The 2024 Kyoto international evidence-based guidelines redefined HRS and WF and stated that surveillance could be discontinued for BD-IPMN tumors ≤ 2 cm in size, if they remain stable during 5 years of follow-up [13]. Nevertheless, discrepancies between guidelines continue to complicate clinical decision-making.

Recent studies demonstrated superior predictive accuracy of artificial intelligence (AI)-based radiomics models, compared to the 2017 Fukuoka guidelines, for identifying malignant IPMN [14]. Moreover, a meta-analysis found that small BD-IPMN lesions that are stable in size during long-term follow-up have an extremely low risk of progression [15]. Unresolved clinical questions remain, including cost-effectiveness of blood- and cyst fluid-derived genetic panels and the optimal timing of surveillance discontinuation (especially in older or frail patients with a reduced life expectancy and/or high surgical risk).

This review aims to re-examine IPMNs from the perspective of their precancerous nature by summarizing recent epidemiologic data and molecular mechanisms; comparing diagnostic and treatment recommendations across major international guidelines; evaluating evidence for imaging and molecular-based risk prediction and surveillance strategies; and suggesting future research directions. The goal is to provide practical evidence to support clinicians in making balanced decisions that avoid overtreatment and undertreatment.

MAIN SUBJECTS

Epidemiology and molecular pathogenesis

With the widespread adoption of abdominal computed tomography (CT) and magnetic resonance imaging (MRI) and the worldwide aging population, incidental detection of pancreatic cystic lesions has increased markedly. Asymptomatic pancreatic cysts are detected in an estimated 11–18% of abdominal imaging studies, with IPMN account-

ing for up to half of these lesions [16,17].

The incidence of IPMN increases with increasing age, exceeding 20% in adults aged ≥ 70 years. Additional risk factors for IPMN include female sex, abdominal obesity, and the presence of renal cysts. The natural history and risk of malignant transformation differ considerably according to IPMN subtype. MD-IPMN and MT-IPMN have been reported to harbor high-grade dysplasia or invasive carcinoma at the time of resection in 40–60% of cases, whereas BD-IPMN tumors have a considerably lower malignancy rate. Long-term observational studies have reported that BD-IPMNs without initial high-risk features have a cumulative malignant transformation rate of approximately 8%, but approximately 25% of these tumors develop imaging-defined WF over time, underscoring the importance of continued surveillance [18].

The molecular pathogenesis of IPMN involves the sequential accumulation of genetic alterations. Early alterations commonly involve dual *KRAS* (70–95%) and *GNAS* (45–80%) mutations. Subsequent genetic events, including inactivation of *RNF43*, *PIK3CA*, and *STK11*, drive progression toward high-grade dysplasia, while additional alterations, such as *TP53* and *SMAD4* mutations, promote progression to invasive carcinoma. Molecular diagnostic tools, such as cfDNA analysis and digital droplet polymerase chain reaction analysis of cyst fluid, have good diagnostic sensitivity (approximately 79%) and very good specificity (98%) for detecting *KRAS* or *GNAS* mutations [9]. Additionally, PancreaSeq Genomic Classifier, a comprehensive NGS panel that simultaneously analyzes 74 genes, has remarkable diagnostic accuracy. It has a 95% sensitivity and 100% specificity, outperforming conventional imaging and clinical assessments [19].

Recent advances in spatial transcriptomics have highlighted subtype-specific molecular signatures: NK6 homeobox 2 acts as a critical differentiation regulator in gastric-type IPMN, correlating with a relatively indolent disease course, whereas pancreatobiliary-type IPMN shows enhanced malignancy potential through increased cell-cycle activity, nuclear factor kappa B (NF-κB) pathway activation, and pancreatic ductal adenocarcinoma (PDAC)-like transcriptional features [20]. Furthermore, a recent digital spatial proteomics study involving 187 IPMN cases characterized subtype-specific landscapes of the nucleotide-binding oligomerization domain–like receptor pyrin domain containing 3 (NLRP3) inflammasome and identified the interleukin (IL)-18/IL-18 binding protein ratio as an independent prognostic marker for invasive IPMN, thus emphasizing the pivotal role of the immune microenvironment in determining progression risk [21].

Thus, current evidence indicates that the risk of malignant transformation is driven by molecular alterations beginning with *KRAS-GNAS* mutations and further influenced by subtype-specific tumor microenvironments. An integrative approach combining imaging characteristics with genomic, transcriptomic, and immunologic biomarkers is essential to effectively stratify risk, minimize unnecessary surgical intervention, and facilitate timely prevention of progression to invasive carcinoma.

Major international/society guidelines: key differences in diagnostic and management recommendations

Clinicians managing IPMN commonly refer to four main sets of guidelines: the 2017 Fukuoka International Association of Pancreatology consensus guidelines; the 2015 American Gastroenterological Association (AGA) guidelines; the 2018 European evidence-based guidelines on pancreatic cystic neoplasms (PCN); and the 2024 Kyoto international evidence-based guidelines. Each guideline is based on different objectives and methodologies and exhibits notable differences in recommendations for surgical indications and surveillance strategies.

Resection criteria

Table 1 summarizes the criteria for surgical resection of IPMN, as outlined in the four main international/society guidelines [11-13,22,23]. Of the four sets of resection criteria, the Fukuoka algorithm is the most aggressive, as it prioritizes sensitivity. The AGA guidelines for resection are more conservative, aiming to minimize costs and complica-

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Table 1. Recommendations of major international guidelines for the management of intraductal papillary mucinous neoplasms

Guideline (publication year)	Surgery versus surveillance recommendations		
	Resection indicated ("high-risk")	Consider surgical resection after evaluation ("intermediate-risk")	Non-surgical management/ surveillance ("low-risk")
Fukuoka (2017) [11]	• Obstructive jaundice • Enhancing mural nodule ≥ 5 mm • MPD diameter ≥ 10 mm • Cytology positive for HGD or malignancy	• Cyst ≥ 3 cm • Thickened enhanced cyst walls • MPD diameter 5–9 mm • Enhancing mural nodule < 5 mm • Abrupt change in pancreatic duct caliber with distal pancreatic atrophy • Lymphadenopathy • Elevated CA 19-9 (> 37 U/ml) • Acute pancreatitis attributable to cyst • Cyst growth rate > 5 mm/2 years	If no surgical indication (absence of "high-risk" or "intermediate-risk" features): • Size-based surveillance stratification • MRI/MRCP every 6–12 months or EUS every 3–6 months • Continue lifelong surveillance with lengthened intervals (up to every 2 years) if cyst remains stable
AGA (2015) [22,23]	Presence of both a solid component and a dilated main pancreatic duct • EUS-FNA confirming HGD or malignancy	If any high-risk feature is present, evaluate with EUS-FNA	If no risk factors: • MRI at 1 year, then every 2 years • Discontinue surveillance after 5 years if stable
European (2018) [12]	Absolute indications for surgery: • Obstructive jaundice • Enhancing mural nodule diameter ≥ 5 mm • MPD diameter ≥ 10 mm • Solid mass • HGD or cancer on FNA cytology	Relative indications for surgery: • Cyst diameter ≥ 40 mm • Enhancing mural nodule < 5 mm • MPD diameter 5–9.9 mm • CA 19-9 > 37 U/ml • Growth ≥ 5 mm/year • New-onset diabetes mellitus or acute pancreatitis Surgery if: • ≥ 1 relative indication(s) and no significant comorbidities • ≥ 2 relative indications and significant comorbidities	If no surgical indication: • MRI every 6 months for 1 year, then annually • Continue lifelong surveillance (as long as the patient remains fit for surgery)
Kyoto (2024) [13]	Presence of any of the following: • Obstructive jaundice • Enhancing mural nodule ≥ 5 mm or solid component • MPD diameter ≥ 10 mm • Positive or suspicious cytology (HGD or IC)	Presence of any of the following "worrisome features": • Cyst diameter ≥ 30 mm • MPD diameter 5–9 mm • Enhancing mural nodule < 5 mm • Thickened/enhancing cyst wall • Acute pancreatitis • Lymphadenopathy • Abrupt change in pancreatic duct caliber with distal pancreatic atrophy • New-onset or worsening diabetes mellitus • Increased CA 19-9 • Cyst growth rate ≥ 2.5 mm/year Presence of any worrisome feature → evaluate with EUS + NGS	If no surgical indication: • Surveillance • If BD-IPMN ≤ 2 cm and stable for 5 years: consider discontinuation or annual lifelong surveillance (due to risk of concomitant pancreatic cancer)

AGA, American Gastroenterological Association; BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; CA 19-9, carbohydrate antigen 19-9; EUS, endoscopic ultrasonography; FNA, fine needle aspiration; HGD, high-grade dysplasia; IC, invasive carcinoma; Kyoto, international evidence-based Kyoto guidelines; MPD, main pancreatic duct; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; NGS, next-generation sequencing.

tions. The European PCN guidelines occupy an intermediate position through their absolute and relative indications approach. The Kyoto 2024 guidelines refine the Fukuoka criteria based on more recent meta-analyses and reduce overtreatment and surveillance burden for small, stable BD-IPMN tumors.

Surveillance interval and discontinuation criteria

Surveillance recommendations for tumors that do not meet the criteria for resection vary between the international/society guidelines (Table 1). The 2017 Fukuoka guidelines recommend surveillance every 3–6 months via endoscopic ultrasonography (EUS) or every 6–12 months via MRI, depending on the lesion size and associated risk factors, with lifelong surveillance as the general principle [11]. The AGA guidelines suggest MRI surveillance 1 year after diagnosis, followed by imaging every 2 years if no risk factors are present. Discontinuation of surveillance is permitted after 5 years if no structural changes occur, with reassessment only if significant changes or high-risk features develop [5,23]. In contrast, the 2018 European PCN guidelines advocate MRI surveillance at 6-month intervals for the first year, followed by annual monitoring indefinitely, as long as the patient remains fit for surgery [12]. The 2024 Kyoto guidelines introduce two notable options for small (≤ 2 cm) BD-IPMN lesions if they remain unchanged with no WF during 5 years of surveillance: discontinue surveillance or continue monitoring at least annually (mainly to detect the emergence of PDAC). Additionally, the Kyoto guidelines recommend postoperative surveillance every 6 months for the first 3 years, followed by annual imaging with CT or MRI and EUS [13].

Diagnostic tools and application of biomarkers

Table 2 shows the general use of diagnostic tools and biomarkers for risk assessment of IPMN. The Kyoto 2024 guidelines are notable for systematically incorporating molecular markers and EUS-fine needle aspiration cytology into their risk stratification model, which was based on a systematic literature review and GRADE methodology.

Table 2. Major international/society guidelines regarding diagnostic tools and biomarker utilization for risk assessment of intraductal papillary mucinous neoplasms

Guideline (publication year)	Test		
	EUS-FNA	Blood biomarkers	Cyst fluid molecular analysis
Fukuoka (2017) [11]	• Recommended if worrisome features present • Cytology serves as adjunctive information	• CA 19-9 (> 37 U/ml) considered as a worrisome feature	Investigational only (research use)
AGA (2015) [22,23]	• Recommended if ≥ 2 high-risk features are present • Emphasis on cost-effectiveness	• Not routinely recommended (low positive predictive value, high cost)	Not recommended (due to high cost, limited reproducibility)
European (2018) [12]	• Actively utilized to guide surgical decision (absolute/relative indications) • Cytology results impact management decisions	• Elevated CA 19-9 (> 37 U/ml) is a relative indication for surgery	Currently investigational (research setting only)
Kyoto (2024) [13]	• Mandatory for evaluating worrisome features • Positive cytology incorporated into high-risk criteria	• Elevated CA 19-9 (> 37 U/ml) recommended for risk assessment • cfDNA/miRNA panels reviewed as potential biomarkers	Recommended as part of risk stratification model (*KRAS*, *GNAS*, *TP53*, *SMAD4*, *CDKN2A*, *PIK3CA*)

AGA, American Gastroenterological Association; CA 19-9, carbohydrate antigen 19-9; cfDNA, cell-free DNA; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; Kyoto, international evidence-based Kyoto guidelines; miRNA, micro RNA.

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Practical points for clinical application

Regarding surgical decision-making, employing a "≥ 2 features" strategy for defining IPMN that warrant surgery can reduce overtreatment, which is especially relevant for older patients with significant comorbidities and high surgical risk. The AGA guidelines recommend surgery if ≥ 2 high-risk features are present, whereas the European PCN guidelines recommend surgery if any absolute indication is present, if ≥ 1 relative indications are present in patients without comorbidities, or if ≥ 2 relative indications are present in patients with significant comorbidities (Table 1). However, a main pancreatic duct (MPD) diameter ≥ 10 mm or obstructive jaundice warrants immediate surgical intervention according to all four major guidelines, leaving little room for variation.

The debate surrounding surveillance duration–discontinuation of monitoring after 5 stable years (AGA) versus lifelong surveillance (European PCN)–has moved toward a middle ground with the Kyoto guidelines, which propose both options for some lesions. The discontinuation option for small BD-IPMN lesions is worthwhile discussing with patients, as prolonged surveillance is associated with significant psychological and financial burden.

The issue of biomarker utilization has also evolved. Despite the cautious stance on cost-effectiveness from the AGA and European PCN, the 2024 Kyoto guidelines grade the assessment of *KRAS* and *GNAS* mutations in cyst fluid as evidence level B, heralding the likely future expansion of molecular diagnostics in clinical practice.

As the major international/society guidelines differ considerably in definitions of lesion risk, criteria for surgery, and surveillance intervals, clear identification of the reference guidelines being used is crucial when designing multicenter research. Cross-referencing criteria, such as HRS versus absolute surgical indications, should be explicitly mapped for comparability.

Imaging and molecular–based risk prediction and surveillance strategies

The primary goal in managing pancreatic IPMN is to precisely identify the minority of tumors at high risk for invasive carcinoma, while simultaneously eliminating unnecessary surgical interventions and prolonged surveillance in the majority of cases. Evidence over the past 3–4 years supports the transition to precision stratification, incorporating multilayered data from imaging morphology, AI-driven radiomics, cyst fluid NGS, liquid biopsy (cfDNA), and serum or cyst fluid protein/enzyme biomarkers. Integrated models and economic evaluations are increasingly being applied to refine risk stratification.

Traditional imaging features, such as mural nodules, MPD dilation, and acute pancreatitis, remain the strongest short-term predictors of high-risk IPMN. A 2023 meta-analysis of 9 cohorts (2,214 surgical cases) identified enhancing mural nodules ≥ 5 mm and MPD diameter ≥ 10 mm as strong risk factors for invasive carcinoma, with odds ratios of 18.7 and 11.9, respectively [24].

Resolving the clinical dilemma of when to surgically intervene versus continuing surveillance hinges on effectively combining morphologic indicators derived from imaging with molecular information obtained from blood and cyst fluid samples. A 2024 multicenter study (n = 3,336; 22,339 person-years follow-up) demonstrated that morphologic variables defined in the 2024 Kyoto guidelines accurately predicted pancreatic cancer occurrence during longer-term follow-up (from 6 months to 10 years). MPD diameter 5–9.9 mm, annual growth ≥ 2.5 mm, and history of acute pancreatitis increased long-term cancer risk by 3.5–5.7-fold, whereas HRS (e.g., enhancing mural nodule ≥ 5 mm, MPD ≥ 10 mm) increased the likelihood of cancer diagnosis within 6 months to nearly 50%. Importantly, the number of WF was directly associated with prognosis, with lesions containing 3–4 WF approaching a 50% cumulative cancer risk over 10 years. This finding provides a robust rationale for shifting from a binary (present/absent) to a quantitative, weighted-scoring approach [17].

Imaging techniques continue to evolve. High-resolution

EUS significantly improves specificity (up to 99%) by detecting subtle nodules < 5 mm and minor wall thickness changes. Deep-learning radiomics can discriminate malignant IPMN based on texture patterns alone, with area under the receiver operating characteristic curve (AUC) values as high as 0.93. However, widespread adoption of this technology awaits the development of standardized equipment and protocols [25,26].

From a molecular perspective, dual *KRAS* and *GNAS* mutations remain the strongest initial predictive events. Cyst fluid NGS panel (PancreaSeq-GC) predicts pathologic high-grade dysplasia or invasive carcinoma with a 95% sensitivity and 100% specificity, thus serving as a valuable adjunctive tool for ambiguous BD-IPMN cases. Additionally, circulating cfDNA methylation signatures demonstrate high diagnostic performance (AUC = 0.89), offering potential noninvasive guidance for long-term surveillance, although cost-effectiveness and reimbursement issues remain unresolved [27,28].

Surveillance strategies translate risk stratification into clinical practice. The revised Kyoto guidelines introduced an option to discontinue surveillance for BD-IPMN ≤ 2 cm that remain stable for 5 years based on evidence showing extremely low cumulative cancer risks at 10 and 15 years (2.7% and 6.1%, respectively). Conversely, lesions with ≥ 3 WF or MPD diameter 7–9 mm warrant intensive monitoring (3–6-month intervals with CT/MRI and annual EUS-cytology/NGS), as their cumulative 10-year cancer risk exceeds 50% [17].

Nevertheless, challenges regarding risk prediction and surveillance strategies remain. First, neither imaging WF nor current molecular markers sufficiently predict synchronous PDAC, necessitating novel screening strategies targeting this specific risk. Second, high-cost technologies, such as NGS and EUS-based confocal imaging, have variable practical applicability (depending on national healthcare financing and equipment availability), highlighting the need for more comprehensive cost-effectiveness analyses. Lastly, AI-based radiomics models currently lack extensive external validation across diverse hospitals and equipment, which will be required for standardized image acquisition and regulatory approval before routine clinical integration.

Future research directions

Future research should focus on expanding precise risk stratification methodologies and developing fully personalized surveillance and intervention plans. For example, the 2024 Kyoto nomogram and algorithms based on the cumulative number of WF were developed and validated mainly with data from Japan [17]. These multimodal models (integrating imaging, clinical, and molecular variables) must be externally validated in international prospective cohorts encompassing diverse populations and clinical environments.

Although recent single-centre studies suggest that AI-radiomics models trained on texture- and shape-based features from CT, MRI, and EUS images can distinguish malignant from benign IPMN with very high apparent accuracy (development-set AUC, 0.93–0.98), early external validations show more modest performance (AUC 0.80–0.89), and real-world prospective efficacy remains under investigation [29-31]. Therefore, standardized image acquisition protocols across devices and vendors, along with harmonized data processing pipelines, are essential before integrating such tools into routine clinical practice.

In the molecular domain, the clinical and economic impacts of the cyst fluid PancreaSeq-GC NGS panel (sensitivity, 95%; specificity, 100%) on surgical decision-making and surveillance intervals should be reassessed in multicenter real-world settings [32]. Furthermore, noninvasive molecular surveillance strategies, such as blood-based cfDNA methylome and proteomics multiplex panels (e.g., the DAY-BREAK study), require validation in large-scale cohorts to demonstrate cost-effectiveness [19].

Regarding surveillance de-escalation, accumulating long-term follow-up data suggest that discontinuing surveillance in older adults with stable BD-IPMN (and no WF or HRS) over a 5-year period is safe [33]. This should be confirmed in randomized controlled trials incorporating patient age, lesion size, and molecular characteristics. For high-risk surgical patients, initial studies report high technical success rates (> 90%) and low severe complication rates (< 10%) for EUS-guided local therapies (e.g., radiofrequency ablation, chemo-photothermal ablation). However, controlled studies

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are required to determine their long-term cancer-preventive effects [34].

Clinical trials targeting subtype-specific tumor immune microenvironments, such as the NLRP3-inflammasome and PD-L1 pathways, are also needed. Additionally, metabolic and genomic signatures capable of detecting synchronous PDAC (which cannot be explained by existing morphologic and molecular indicators) require further investigation.

CONCLUSION

IPMN represents a precancerous lesion that can precede pancreatic cancer, yet not all lesions have equal malignant potential. Over the past 2 decades, epidemiologic, molecular, and imaging research, combined with iterative updates of international/society guidelines, have improved our understanding of various issues: differences in malignancy risk between IPMN subtypes; multistage molecular progression, beginning with *KRAS* and *GNAS* mutations; hierarchical significance of morphologic and clinical indicators of cancer risk (e.g., mural nodules, MPD dilation, faster growth rate, CA 19-9); and the emerging clinical value of advanced technologies, including NGS, AI-radiomics, and liquid biopsy. The 2024 Kyoto guidelines introduced the first evidence-based roadmap for reducing overtreatment by integrating WF number and cyst fluid NGS/cytology results into risk assessment, while also allowing discontinuation of surveillance for small (≤ 2 cm) BD-IPMN lesions that remain stable for 5 years.

The challenge for clinicians is to incorporate this evolving knowledge into clinical practice and research design through "risk-adaptive" protocols. Specifically, this includes externally validating multidimensional nomograms that integrate imaging-based WF, molecular biomarkers, and AI-based scores, embedding them into routine clinical workflows; significantly reducing surveillance intensity for patients with ultra-low-risk BD-IPMN; and establishing early surgical intervention or alternative treatments, such as EUS-guided local therapies, for patients with multiple WF or molecular-positive high-risk lesions, through clinical trials. Concurrently, efforts must continue to identify novel metabolic and genomic signatures for detecting synchronous PDAC arising independently from existing IPMN and to develop immune-preventive strategies targeting subtype-specific tumor immune microenvironments.

In summary, the key to IPMN management involves achieving a balance between overtreatment and undertreatment. By systematically applying imaging assessment, molecular diagnostics, and risk stratification, tailored surveillance and intervention strategies can be developed. The ultimate goal is to develop precision onco-prevention models that effectively reduce progression to invasive pancreatic cancer, while minimizing burdens on patients and healthcare resources.

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CONFLICTS OF INTEREST

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