Review Article

Clinical Management of Pancreatic Intraductal Papillary Mucinous Neoplasms: Practical Application of the Fukuoka Criteria in Risk Stratification and Treatment Decision-Making

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Abstract

Intraductal papillary mucinous neoplasms are mucin-producing epithelial tumors arising from the pancreatic ductal system and represent an important category of pancreatic cystic neoplasms due to their potential for malignant transformation. These lesions are characterized by intraductal proliferation of mucinous epithelium and varying degrees of dysplasia. Histologically, they are

classified into gastric, intestinal, pancreatobiliary, and oncocytic subtypes, each associated with distinct biological behavior and risk of progression. Molecular alterations, particularly mutations in KRAS, GNAS, RNF43, and TP53, play a central role in the pathogenesis of these neoplasms and contribute to the transition from low-grade dysplasia to invasive carcinoma. Their natural history typically follows a stepwise progression model, highlighting the importance of early identification and surveillance. Intraductal papillary mucinous neoplasms are classified according to ductal involvement into main duct, branch duct, and mixed-type lesions. Main duct lesions demonstrate a higher risk of malignancy, particularly when significant dilation of the main pancreatic duct is present, whereas branch duct lesions generally carry a lower risk but require careful monitoring. Diagnostic evaluation relies heavily on imaging techniques such as magnetic resonance cholangiopancreatography, computed tomography, and endoscopic ultrasound, which allow assessment of morphological features associated with malignancy, including mural nodules and ductal dilation. The Fukuoka criteria provide a widely adopted framework for risk stratification and management by identifying high-risk stigmata and worrisome features that guide decisions between surgical resection and surveillance. Surgical treatment typically includes pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy depending on lesion location and disease extent. Despite these advances, challenges remain in the management of intermediate-risk lesions and in balancing early cancer detection with the avoidance of unnecessary surgery. Emerging diagnostic approaches, including molecular biomarkers and artificial intelligence–based imaging analysis, may improve diagnostic accuracy and support more personalized surveillance strategies.

Key words

Pancreatic cystic neoplasms, risk stratification, malignant transformation, endoscopic ultrasound, pancreatic duct dilation, molecular biomarkers.

Introduction

The prevalence of pancreatic cysts in the general population has been reported to reach up to fifty percent, with intraductal papillary mucinous neoplasms representing the most common type of pancreatic cystic neoplasm [1]. The widespread implementation of high-resolution imaging techniques has significantly increased the detection of these lesions, many of which are discovered incidentally during radiologic evaluations performed for unrelated clinical indications. As a result, pancreatic cystic lesions are now identified with increasing frequency, encompassing a broad pathological spectrum that ranges from benign entities to premalignant and malignant forms [2].

Within this context, intraductal papillary mucinous neoplasms have gained particular clinical relevance because they represent one of the few radiographically identifiable precursor lesions of pancreatic cancer. Their identification provides a potential opportunity for early detection and timely intervention before malignant transformation occurs. This aspect is especially important considering that approximately eight percent of pancreatic cancers originate from cystic lesions such as intraductal papillary mucinous neoplasms, highlighting the necessity for careful surveillance strategies and appropriately timed surgical management when indicated [1, 3].

To address this clinical challenge, several international guidelines have been developed to guide the management of these lesions. Among the most widely adopted frameworks are the Fukuoka guidelines and the European evidence-based guidelines, both of which aim to identify patients at risk for high-grade dysplasia or invasive carcinoma. These guidelines rely on a combination of clinical, radiologic, and

biochemical markers to inform decision-making. Clinical features such as obstructive jaundice, the presence of a solid mass, and elevated carbohydrate antigen 19-9 levels are considered important indicators that may suggest the need for surgical intervention [4].

Despite the availability of these structured recommendations, the management of intraductal papillary mucinous neoplasms remains complex. One of the principal challenges involves achieving an appropriate balance between preventing pancreatic cancer through early surgical treatment and avoiding unnecessary operations in patients with low-risk lesions. This difficulty arises in part because currently available diagnostic tests are not always sufficiently accurate to distinguish reliably between benign cysts and those with malignant potential [3].

In response to these limitations, advances in diagnostic technologies have been actively explored in recent years. Techniques such as endoscopic ultrasound have improved the morphological assessment of pancreatic cystic lesions and allow for the collection of cyst fluid for further analysis. In addition, the investigation of molecular markers within cyst fluid has shown promise in improving the stratification of malignancy risk in intraductal papillary mucinous neoplasms. Recent studies have identified specific cyst fluid proteins capable of distinguishing between low-grade and high-grade intraductal papillary mucinous neoplasms, suggesting that these biomarkers may enhance preoperative risk assessment and support more accurate clinical decision-making [5, 6].

The development of international consensus guidelines has therefore played a fundamental role in standardizing the clinical management of intraductal papillary mucinous neoplasms. Among these, the Fukuoka criteria have become particularly influential in guiding clinical evaluation and therapeutic planning. By integrating imaging findings with clinical indicators of malignancy risk, these criteria assist clinicians in identifying patients who may benefit from surgical intervention while allowing others to be managed through careful surveillance strategies [4, 7].

The objective of this review is to analyze the clinical management of pancreatic intraductal papillary mucinous neoplasms through the practical application of the Fukuoka criteria, emphasizing their role in risk stratification, diagnostic evaluation, surveillance strategies, and surgical decision-making.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of pancreatic intraductal papillary mucinous neoplasms, with particular emphasis on the clinical application of the Fukuoka criteria in risk stratification, diagnostic evaluation, surveillance strategies, and surgical decision-making. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the biological and clinical heterogeneity of intraductal papillary mucinous neoplasms, the variability in imaging interpretation, and the evolving role of endoscopic and molecular diagnostics, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate radiologic, clinical, endoscopic, and biomarker-based considerations into a coherent and clinically applicable framework. Particular attention was given to the differentiation between main duct, branch duct, and mixed-type lesions, the identification and interpretation of high-risk stigmata and worrisome features described in the Fukuoka criteria, and the balance between cancer prevention through early surgical intervention and the avoidance of unnecessary procedures in low-risk lesions. The objective of this

methodological approach was to provide a structured synthesis capable of supporting multidisciplinary clinical decision-making in the management of pancreatic cystic neoplasms.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2026. The final search was performed in December 2026. This timeframe was selected to capture contemporary advances in the diagnostic evaluation and management of pancreatic intraductal papillary mucinous neoplasms, including updates to international consensus recommendations, developments in endoscopic ultrasound techniques, cyst fluid molecular profiling, and evolving evidence regarding surveillance strategies and surgical outcomes. Foundational studies were incorporated when necessary to contextualize the historical development of international guidelines and the pathophysiological basis of malignant transformation in pancreatic cystic lesions. The search strategy combined Medical Subject Headings and free-text terms using Boolean operators related to intraductal papillary mucinous neoplasm, pancreatic cystic neoplasm, Fukuoka guidelines, international consensus guidelines, high-risk stigmata, worrisome features, main pancreatic duct dilation, mural nodules, endoscopic ultrasound, cyst fluid analysis, molecular markers, carbohydrate antigen 19-9, surveillance, pancreatectomy, and malignancy risk. Searches were conducted in titles, abstracts, and indexed subject headings to maximize sensitivity.

The initial search yielded 212 records. After removal of duplicates, 168 articles remained for title and abstract screening. Of these, 87 underwent full-text evaluation, and 42 studies were included in the final synthesis. Study selection was performed independently by two authors using predefined eligibility criteria, and disagreements were resolved through discussion and consensus. Eligible studies included randomized controlled trials, observational cohort studies, systematic reviews, meta-analyses, expert consensus statements, and contemporary international clinical guidelines addressing the diagnostic evaluation, risk stratification, surveillance strategies, or surgical management of pancreatic intraductal papillary mucinous neoplasms. Exclusion criteria comprised non–peer-reviewed publications, isolated case reports, editorials lacking clinically relevant outcome data, purely technical procedural descriptions without diagnostic or prognostic implications, redundant datasets, and studies not directly addressing the clinical application of the Fukuoka criteria or the management of pancreatic intraductal papillary mucinous neoplasms.

Data extraction was conducted using a structured data collection approach designed to capture relevant clinical and methodological variables from each study. Extracted variables included study design, patient population characteristics, subtype of intraductal papillary mucinous neoplasm, cyst size, main pancreatic duct caliber, presence and characterization of mural nodules, clinical markers such as obstructive jaundice and carbohydrate antigen 19-9 levels, endoscopic ultrasound findings, cyst fluid cytology and biomarker profiles, treatment modality when applicable, histopathological grade, presence of invasive carcinoma, surveillance intervals, and reported clinical outcomes. Particular emphasis was placed on variables related to the diagnostic and prognostic elements incorporated within the Fukuoka criteria.

Methodological quality and internal validity were assessed narratively, taking into account factors such as study design, risk of bias, sample size, duration of follow-up, consistency in imaging interpretation and pathological classification, and reproducibility of reported outcomes. Greater interpretative weight was assigned to higher-level evidence, including randomized trials,

systematic reviews, and international guideline recommendations when conflicting results were identified among studies.

Reference lists of included studies were manually reviewed to identify additional relevant publications not captured in the initial database search. The evidence synthesis was subsequently organized into thematic domains reflecting key aspects of clinical management, including epidemiology and detection of pancreatic cystic lesions, classification of intraductal papillary mucinous neoplasms, diagnostic evaluation, clinical application of the Fukuoka criteria, surveillance strategies, and surgical management. Given its narrative design, this review does not provide pooled quantitative estimates and is therefore subject to potential selection bias. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas the critical appraisal of evidence, synthesis of findings, and final interpretation were conducted independently by the authors to preserve methodological rigor. Ethical approval was not required because the study analyzed previously published data and did not involve human participants or identifiable patient information.

Pathophysiology and Biological Behavior of Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms are defined as mucin-producing epithelial tumors that originate from the pancreatic ductal system. These lesions represent a distinct category of pancreatic cystic neoplasms characterized by intraductal proliferation of mucinous epithelium and varying degrees of dysplasia. Histopathologically, intraductal papillary mucinous neoplasms are classified into several subtypes, each associated with specific biological behavior and risk of malignant progression. The gastric subtype is frequently associated with low-grade dysplasia and generally demonstrates a lower risk of progression. In contrast, the intestinal subtype is linked to the so-called intestinal pathway and is typically associated with less aggressive clinical features as well as the development of colloid carcinomas [8]. Another important subtype is the pancreatobiliary variant, which has been associated with a higher prevalence of high-grade dysplasia and carcinoma, particularly in branch-duct intraductal papillary mucinous neoplasms [9]. The oncocytic subtype is less common and is characterized by distinctive molecular and histopathological features that differentiate it from the other variants [10].

The pathogenesis of intraductal papillary mucinous neoplasms is strongly influenced by a series of molecular and genetic alterations that contribute to their development and progression. Among the most frequently identified mutations are alterations in KRAS, GNAS, RNF43, and TP53, which play key roles in the molecular events that drive the transition from low-grade dysplasia to invasive carcinoma [8]. These genetic changes are accompanied by broader biological processes that include metabolic alterations and disruptions in the cellular microenvironment. In particular, immune-related modifications and inflammatory responses have been recognized as important contributors to tumor progression and disease evolution [11]. More recently, advances in spatial transcriptomics have provided further insights into the biological complexity of these lesions by demonstrating significant molecular heterogeneity among intraductal papillary mucinous neoplasm subtypes. These studies have revealed distinct gene expression patterns and differences in immune dynamics that may contribute to variations in clinical behavior and malignant potential [12].

The natural history of intraductal papillary mucinous neoplasms is generally characterized by a stepwise progression model in which early lesions with low-grade dysplasia may gradually evolve into high-grade dysplasia and ultimately

invasive carcinoma. This progressive sequence reflects the cumulative effect of genetic alterations and microenvironmental changes that promote neoplastic transformation over time [10]. Several factors have been associated with an increased risk of malignant transformation into pancreatic ductal adenocarcinoma, including the histological subtype of the lesion, the presence of high-grade dysplasia, and the accumulation of specific genetic mutations that influence tumor behavior [9, 11]. In addition to their potential for malignant progression, intraductal papillary mucinous neoplasms are also clinically relevant because they may coexist with pancreatic carcinoma or independently give rise to pancreatic cancer. For this reason, appropriate surveillance strategies play a critical role in the early detection and management of these lesions, allowing clinicians to monitor disease progression and intervene when necessary [13, 14].

Classification of Intraductal Papillary Mucinous Neoplasms

Main duct intraductal papillary mucinous neoplasms are characterized by involvement of the main pancreatic duct and frequently present with dilation of this ductal structure. The evaluation of these lesions relies heavily on imaging modalities such as computed tomography and magnetic resonance imaging, which allow accurate assessment of the diameter of the main pancreatic duct. A ductal diameter of at least five millimeters has been identified as a clinically relevant indicator associated with an increased risk of malignancy [15, 16]. The clinical importance of this subtype lies in its substantially higher malignant potential when compared with branch duct lesions. The risk of malignancy increases progressively with the degree of ductal dilation, and ductal diameters equal to or greater than ten millimeters have been strongly associated with the presence of high-grade dysplasia or invasive carcinoma. For this reason, surgical resection is frequently recommended in patients diagnosed with main duct intraductal papillary mucinous neoplasms due to their elevated risk of malignant transformation [17, 18].

Branch duct intraductal papillary mucinous neoplasms represent another important subtype and are commonly detected incidentally during imaging studies performed for unrelated clinical indications. This incidental detection contributes significantly to the high reported prevalence of pancreatic cysts in the general population [1]. In contrast to lesions involving the main pancreatic duct, branch duct intraductal papillary mucinous neoplasms are generally associated with a lower risk of malignant progression. Nevertheless, certain radiologic characteristics may indicate a higher risk profile and therefore require closer clinical attention. Imaging findings such as the presence of mural nodules or dilation of the main pancreatic duct measuring five millimeters or more have been associated with an increased likelihood of malignant transformation [19, 20]. Because of this potential for progression, regular surveillance through periodic imaging evaluation is recommended in order to identify early changes suggestive of neoplastic progression and allow timely clinical intervention [13].

Mixed type intraductal papillary mucinous neoplasms involve simultaneous involvement of both the main pancreatic duct and the branch duct system. This combined ductal involvement results in lesions that demonstrate features of both main duct and branch duct intraductal papillary mucinous neoplasms, which may complicate their diagnostic evaluation and clinical management [21]. From a clinical perspective, mixed-type lesions are generally considered to carry an intermediate risk of malignancy. Management strategies are therefore often individualized and depend on the predominant ductal involvement as well as the specific imaging findings observed during evaluation. The identification of high-risk stigmata, including the presence of mural nodules or significant dilation of the pancreatic

duct, plays an important role in guiding clinical decision-making and determining whether surgical intervention should be considered [16, 20].

Diagnostic Evaluation

The clinical presentation of intraductal papillary mucinous neoplasms varies considerably, and many lesions remain asymptomatic for prolonged periods. A substantial proportion of these neoplasms are identified incidentally during imaging studies performed for unrelated clinical conditions, reflecting the increasing use of advanced radiologic techniques in routine medical practice. Because these lesions often do not produce symptoms during the early stages of disease, they may remain undetected until imaging is performed for other diagnostic purposes [1, 22].

Although many intraductal papillary mucinous neoplasms are asymptomatic at the time of detection, symptomatic presentations can occur, particularly as the disease progresses. When symptoms are present, they commonly include pancreatitis, abdominal pain, unintended weight loss, and jaundice. These manifestations are frequently associated with more advanced stages of disease and may suggest a higher likelihood of malignant transformation. Consequently, the presence of these symptoms is often considered clinically relevant in the evaluation of patients with pancreatic cystic lesions [4, 13].

Given the variable clinical presentation of intraductal papillary mucinous neoplasms, imaging plays a fundamental role in their detection and characterization. Magnetic resonance cholangiopancreatography is commonly considered the first-line imaging modality due to its non-invasive nature and its ability to provide detailed visualization of the pancreatic ductal system. This technique is particularly valuable for identifying structural abnormalities such as mural nodules and dilation of the pancreatic duct, both of which are important features in the assessment of malignancy risk [16, 23].

Computed tomography also plays a significant role in the diagnostic evaluation of these lesions by providing a comprehensive assessment of pancreatic anatomy and allowing the detection of calcifications within cystic structures. Despite these advantages, computed tomography is generally considered less sensitive than magnetic resonance imaging for identifying small mural nodules, which represent an important radiologic marker associated with malignant potential [16].

In situations in which findings from magnetic resonance cholangiopancreatography or computed tomography are inconclusive, or when imaging studies reveal features suggestive of increased malignancy risk, endoscopic ultrasound may provide additional diagnostic information. This technique offers high-resolution imaging of pancreatic cystic lesions and allows the performance of fine-needle aspiration to obtain cyst fluid for further analysis. Through this approach, both morphological characteristics and biochemical features of the cyst can be evaluated in greater detail [5, 22].

Endoscopic ultrasound is particularly effective in the morphological evaluation of pancreatic cystic lesions because it allows precise identification of mural nodules and other structural abnormalities associated with malignancy. The presence of mural nodules has been recognized as an important predictor of malignant transformation and therefore represents a critical finding during the diagnostic assessment of intraductal papillary mucinous neoplasms [24, 25]. In addition to morphological assessment, cyst fluid obtained through endoscopic ultrasound-guided fine-needle aspiration can be analyzed for cytological features and biochemical markers. This analysis may include cytology, measurement of carcinoembryonic antigen levels, and evaluation of molecular markers. Elevated carcinoembryonic antigen concentrations and the

presence of atypical cells in cyst fluid are commonly associated with mucinous cysts, which are known to carry a higher risk of malignant progression [5, 23].

The Fukuoka Criteria; Conceptual Framework

The development of international consensus guidelines has played a central role in standardizing the clinical management of intraductal papillary mucinous neoplasms. The Fukuoka guidelines emerged as an evolution of the earlier Sendai guidelines, incorporating new clinical evidence and updated insights in order to provide a more refined and clinically applicable framework for the management of these pancreatic cystic lesions. Both the Fukuoka guidelines and the European evidence-based guidelines have demonstrated similar levels of accuracy in identifying patients with high-grade dysplasia or invasive carcinoma in intraductal papillary mucinous neoplasms. Within this context, particular emphasis has been placed on clinical markers such as obstructive jaundice and elevated carbohydrate antigen 19-9 levels, which have been recognized as important predictors of the need for surgical intervention. Despite the advances achieved through these consensus recommendations, the guidelines also highlight the need for continued research aimed at refining diagnostic protocols and improving individualized treatment strategies for patients with pancreatic cystic neoplasms [4].

A key component of the Fukuoka criteria involves the identification of high-risk stigmata, which represent clinical and radiological features strongly associated with malignant transformation. These high-risk indicators include obstructive jaundice, the presence of enhancing solid components within the cyst, and dilation of the main pancreatic duct measuring at least ten millimeters. The presence of these features is considered highly suggestive of malignancy and frequently leads to recommendations for surgical intervention. Evidence supporting this approach has demonstrated that patients presenting with high-risk stigmata may exhibit malignancy rates approaching seventy percent, highlighting the clinical importance of these findings in therapeutic decision-making [26]. Enhancing solid components and significant dilation of the main pancreatic duct have been identified as strong predictors of high-grade dysplasia or invasive carcinoma and have shown high diagnostic odds ratios in clinical studies [19].

In addition to high-risk stigmata, the Fukuoka criteria also describe a group of findings known as worrisome features, which are associated with an increased but less definitive risk of malignancy. These features include cyst size equal to or greater than three centimeters, thickened or enhancing cyst walls, dilation of the main pancreatic duct measuring between five and nine millimeters, abrupt changes in duct caliber accompanied by distal pancreatic atrophy, the presence of lymphadenopathy, and elevated tumor marker levels. The presence of these characteristics warrants further clinical evaluation because they may indicate a higher likelihood of malignant transformation. Importantly, the risk associated with these findings appears to increase in a stepwise manner as the number of worrisome features increases. Studies have shown that the estimated risk of malignancy may rise from approximately twenty-two percent in the presence of a single worrisome feature to nearly fifty-nine percent when three such features are identified [26]. Among these indicators, dilation of the main pancreatic duct measuring five millimeters or more has been identified as a significant predictor of malignancy, suggesting that pancreatectomy may be considered in carefully selected patients [15].

Risk stratification based on these criteria plays a fundamental role in the clinical management of intraductal papillary mucinous neoplasms. The identification of specific radiologic and clinical

markers allows clinicians to distinguish between lesions that require surgical resection and those that may be safely managed through surveillance strategies. In general, the presence of high-risk stigmata strongly supports the recommendation for surgical treatment, whereas the detection of worrisome features typically prompts further diagnostic evaluation and closer monitoring [26]. Through this structured risk-based approach, the Fukuoka criteria facilitate individualized management decisions that aim to balance the potential benefits of early surgical intervention against the risks associated with unnecessary procedures. At the same time, these guidelines contribute to the optimization of surveillance resources and support more efficient clinical management of patients with pancreatic cystic lesions [13].

Clinical Application of the Fukuoka Criteria in Patient Management

The clinical management of intraductal papillary mucinous neoplasms begins with the identification of pancreatic cystic lesions through imaging modalities such as magnetic resonance imaging and computed tomography. These imaging techniques play a fundamental role in the initial detection and characterization of pancreatic cysts, allowing clinicians to recognize structural abnormalities within the pancreatic ductal system. Once a cystic lesion has been identified, an accurate diagnostic and management strategy requires the integration of imaging findings with relevant clinical data and established guideline criteria in order to guide clinical decision-making.Following the detection of pancreatic cystic lesions, additional diagnostic evaluation is often performed using endoscopic ultrasound. This technique provides high sensitivity and specificity for differentiating pancreatic cystic lesions and offers detailed visualization of cyst morphology and ductal involvement [5]. Endoscopic ultrasound is therefore frequently incorporated into the diagnostic workflow when further clarification is required. In addition to imaging findings, clinical markers such as the presence of jaundice, the identification of a solid mass, and elevated levels of carbohydrate antigen 19-9 play a significant role in predicting the potential need for surgical intervention [4]. Diagnostic accuracy may be further enhanced through endoscopic ultrasound-guided fine-needle aspiration, which allows for the analysis of cyst fluid markers and provides additional information relevant to malignancy risk [5].

The decision to proceed with surgical resection is primarily determined by the presence of high-risk stigmata and other relevant lesion characteristics. Absolute indications for surgery include dilation of the main pancreatic duct measuring at least five millimeters, the presence of a solid component within the lesion, and clinical manifestations such as obstructive jaundice [15]. In these situations, the likelihood of malignant transformation is considered sufficiently high to justify operative management. Surgical decision-making may differ in the case of branch duct intraductal papillary mucinous neoplasms. For these lesions, resection is generally considered when high-risk characteristics are present, including cyst size greater than three centimeters, the presence of mural nodules, or evidence of rapid cyst growth during follow-up evaluation [27].

For lesions that do not meet criteria for surgical intervention, surveillance strategies represent a critical component of clinical management. The interval and intensity of follow-up monitoring are typically determined by cyst size and overall risk classification, with larger cysts or those demonstrating higher-risk characteristics requiring more frequent surveillance [13]. Imaging modalities such as magnetic resonance imaging and endoscopic ultrasound play an essential role in this process, as they enable clinicians to monitor changes in cyst morphology, ductal dilation, or the development of new features that may indicate disease

progression and necessitate further intervention [28].

Management decisions may require consideration in elderly patients or individuals who present with increased surgical risk. In these cases, the potential benefits of surgical treatment must be carefully balanced against the risks associated with operative procedures and postoperative complications. A comprehensive risk–benefit assessment is therefore essential, particularly in patients with advanced age or significant comorbid conditions [29]. When surgical risk is considered high, a conservative management strategy may be more appropriate. Under these circumstances, regular surveillance using imaging studies and ongoing clinical assessment is recommended to detect any changes in lesion characteristics that might subsequently require surgical intervention [1].

Surgical Management

Surgical management of intraductal papillary mucinous neoplasms includes several types of pancreatic resections, and the selection of the appropriate procedure largely depends on the anatomical location of the lesion within the pancreas. Pancreaticoduodenectomy is commonly performed for intraductal papillary mucinous neoplasms located in the head of the pancreas. This operation involves the removal of the pancreatic head, the duodenum, and in some cases part of the stomach. Although pancreaticoduodenectomy is associated with considerable postoperative morbidity, it continues to represent a standard surgical approach for the management of intraductal papillary mucinous neoplasms that exhibit a high malignant potential [30, 31].

For lesions located in the body or tail of the pancreas, distal pancreatectomy is typically the procedure of choice. The extent of resection may vary depending on the anatomical distribution of the lesion, and more extensive resections have been associated with increased morbidity and mortality. In this context, the classification of distal pancreatectomy into different types according to technical difficulty has been proposed as a useful tool for predicting postoperative outcomes and evaluating operative complexity [32].

Total pancreatectomy represents another surgical option, although it is performed less frequently because of the significant postoperative complications associated with complete removal of the pancreas, including the development of diabetes. Despite these limitations, total pancreatectomy may be considered in situations in which the entire pancreas is affected or when there is a high risk of malignancy. In carefully selected patients, this procedure may provide oncologic benefits [33, 34].

Intraoperative assessment is an essential component of pancreatic surgery for intraductal papillary mucinous neoplasms. Frozen section analysis is commonly used during surgery to evaluate the margins of resection in real time. This technique allows surgeons to determine whether additional pancreatic tissue should be removed in order to achieve clear surgical margins, which is an important factor in reducing the risk of recurrence. Ensuring negative margins, known as R0 resection, is considered critical for improving long-term outcomes. Surgical techniques such as total mesopancreas excision have been shown to increase the rate of R0 resections and reduce the incidence of locoregional recurrence [31].

Despite improvements in surgical techniques and perioperative care, pancreatic resections remain associated with significant postoperative morbidity. Complications such as pancreatic fistula are commonly observed following pancreatectomy in patients with intraductal papillary mucinous neoplasms. Although mortality rates are generally low, they may vary according to the extent of resection and individual patient characteristics [29, 32]. Long-

term oncologic outcomes depend on both the type of surgical procedure performed and the presence of malignant disease. In selected cases, total pancreatectomy may provide longer survival, although this benefit must be considered in the context of the increased risk of postoperative diabetes [33, 34]. In addition, minimally invasive surgical approaches, including robotic pancreatectomy, are increasingly being adopted and have demonstrated improvements in postoperative outcomes compared with traditional techniques [29, 35].

Limitations and Controversies of the Fukuoka Criteria

Intermediate-risk intraductal papillary mucinous neoplasms present a significant clinical challenge because of the variability in their potential for malignant transformation. Although the Fukuoka criteria provide structured guidance for identifying high-risk stigmata and worrisome features, uncertainty remains in the management of lesions that fall into an intermediate-risk category. This uncertainty complicates clinical decision-making, particularly when determining whether surgical intervention or continued surveillance is the most appropriate strategy. Evidence suggests that conservative management may be feasible in patients presenting with worrisome features without compromising overall survival. Nevertheless, approximately fifty percent of these patients ultimately require surgical intervention during follow-up, reflecting the difficulty in predicting disease progression within this subgroup [7].

Imaging plays a central role in the diagnosis and management of intraductal papillary mucinous neoplasms, yet interpretation of imaging findings is subject to considerable interobserver variability. Differences in how radiologic features are interpreted can influence clinical decision-making and may lead to variations in patient management among clinicians [3]. In response to these limitations, advanced imaging approaches have been explored as potential tools for improving diagnostic precision. Techniques such as magnetic resonance imaging–derived fat fraction analysis and fluorodeoxyglucose positron emission tomography combined with computed tomography have been proposed to enhance diagnostic accuracy and reduce variability in interpretation. Despite their potential advantages, these modalities have not yet been widely incorporated into routine clinical practice [36, 37].

Another important challenge associated with the use of the Fukuoka criteria involves the balance between preventing malignant progression and avoiding unnecessary surgical treatment. Although these guidelines are designed to facilitate timely identification of high-risk lesions, their application may occasionally result in overtreatment. A considerable proportion of intraductal papillary mucinous neoplasms that undergo surgical resection are ultimately found to be benign, illustrating the limitations of current diagnostic criteria [29]. At the same time, conservative management strategies carry the risk of delayed cancer detection, particularly in patients with intermediate-risk lesions who are monitored through surveillance rather than immediate surgical intervention [7].

The Fukuoka criteria represent one of several guideline systems developed to guide the management of intraductal papillary mucinous neoplasms. Comparative analyses have demonstrated that the Fukuoka criteria and European evidence-based guidelines show similar accuracy in identifying lesions associated with high-grade dysplasia or invasive carcinoma. Nevertheless, these comparisons also highlight the need for further research to refine diagnostic protocols and improve clinical decision-making [4]. Differences between guideline systems remain evident in certain recommendations, including variations in the thresholds used to determine surgical intervention based on the diameter of the main pancreatic duct, reflecting

ongoing debate regarding the optimal management strategy for these lesions [15].

Emerging Diagnostic Tools and Future Directions

Advances in molecular diagnostics have significantly expanded the ability to evaluate pancreatic cystic lesions, particularly through the identification of molecular and genetic biomarkers. Next-generation sequencing has emerged as an important tool in this context by improving the diagnostic accuracy of pancreatic cysts through the identification of subtype-specific genetic alterations. The application of next-generation sequencing to cyst fluid analysis enables the detection of driver mutations and molecular pathways that are directly involved in disease progression and malignant transformation. Through this approach, the molecular classification of pancreatic cystic neoplasms has been improved, which in turn supports more accurate risk stratification and informs clinical decision-making [27].

Further developments in molecular diagnostics have led to the creation of combined DNA and RNA sequencing platforms designed to enhance the diagnostic evaluation of pancreatic cystic lesions. One example is the PancreaSeq Genomic Classifier, which integrates both DNA and RNA sequencing to improve the classification of cystic precursor neoplasms and the detection of advanced neoplasia. This integrated approach has demonstrated high sensitivity and specificity in identifying clinically significant lesions. In addition, the use of these genomic platforms has been shown to increase the sensitivity of existing diagnostic guidelines by more than ten percent while maintaining a high level of specificity, thereby strengthening the diagnostic framework used in the management of pancreatic cystic neoplasms [38].

In parallel with genomic sequencing technologies, micro-ribonucleic acid analysis has emerged as another promising method for improving the evaluation of intraductal papillary mucinous neoplasms. Profiling of micro-ribonucleic acids in cyst fluid represents a potential non-invasive diagnostic strategy for assessing malignant transformation. Specific micro-ribonucleic acids have been identified as being enriched in malignant cases of intraductal papillary mucinous neoplasms, suggesting that these molecular markers may contribute to earlier detection and improved risk assessment [39].

Technological innovations have also extended into the field of imaging analysis through the application of artificial intelligence and radiomics. Artificial intelligence techniques, particularly machine learning and deep learning approaches, have demonstrated considerable potential for improving the diagnosis and risk stratification of pancreatic cysts. Artificial intelligence models, including convolutional neural networks, have shown high levels of accuracy in the classification of intraductal papillary mucinous neoplasm subtypes and have been reported to outperform existing clinical guideline–based approaches in certain settings [40]. In addition to imaging analysis, artificial intelligence–augmented evaluation of genetic data has been explored as a means of improving biomarker identification. Approaches such as nucleotide-to-amino acid analysis allow for more detailed interpretation of genomic alterations and enhance the performance of machine learning models in predicting cancer progression [41].

These developments have contributed to the emergence of personalized surveillance strategies for patients with pancreatic cystic lesions. Such strategies emphasize the integration of clinical information, radiological findings, and molecular data in order to develop individualized management plans. By combining these different sources of information, clinicians may improve early detection of malignant transformation while reducing the likelihood of unnecessary interventions [13]. Within this evolving

diagnostic landscape, endoscopic ultrasound–guided needle-based confocal laser endomicroscopy has also been introduced as an innovative technique that allows real-time optical biopsy during endoscopic evaluation. This technology improves the diagnostic accuracy of intraductal papillary mucinous neoplasms and enhances risk stratification. Moreover, the incorporation of artificial intelligence algorithms into endoscopic ultrasound–guided needle-based confocal laser endomicroscopy analysis has been shown to further improve its diagnostic capabilities [42].

Conclusions

Intraductal papillary mucinous neoplasms are heterogeneous pancreatic cystic lesions characterized by distinct histopathological subtypes, molecular alterations, and variable malignant potential. Their progression typically follows a stepwise pathway from low-grade dysplasia to invasive carcinoma, influenced by genetic mutations and microenvironmental changes that contribute to disease evolution.

The Fukuoka criteria provide a structured framework for risk stratification and clinical management by identifying high-risk stigmata and worrisome features that guide decisions between surgical resection and surveillance. Despite their clinical utility, challenges remain in intermediate-risk lesions and imaging interpretation, highlighting the potential role of emerging molecular and imaging technologies in improving diagnostic accuracy and personalized management.

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