REVIEW ARTICLE

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Pancreatic Cysts

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CME

Cystic lesions of the pancreas were once considered to be rare and of uncertain clinical significance, as reported in the *Journal* in 1934.[1] Over subsequent decades, these lesions came to be recognized as more common than previously thought and potentially premalignant entities that warrant concern. Imaging studies have shown a prevalence ranging from 2 to 15%, and some autopsy data suggest a prevalence as high as 50%.[2-6] The incidence of pancreatic cysts is on the rise, even when expanded use of imaging is taken into account, and increases with age.[7] However, most cysts are benign; only a subset has malignant potential. The terms mucinous cystic neoplasm and intraductal papillary neoplasm were introduced in 1996 to describe the most common premalignant cysts.[8-14]

The overall risk of malignancy in pancreatic cysts may be as low as 0.5 to 1.5%, and the annual risk of progression is 0.5%.[7,15] Conversely, studies estimate that 15% of all pancreatic adenocarcinomas originate from mucinous cysts, and these cysts are the sole recognizable precursors of malignant transformation that can be identified on cross-sectional imaging.[16-18] Thus, identification of cysts at risk for progression provides an opportunity for prevention or early detection of cancer. Although surgical resection is the only curative treatment option, it carries a risk of major complications, despite technical advances.

Over the past two decades, several guidelines for the management of pancreatic cysts have been published, which primarily rely on expert opinion.[9-14] The challenge of cyst management lies in recognizing high-risk lesions and offering surgical resection before the development of invasive cancer.[19,20] This objective must be carefully weighed against the fact that benign and low-risk cysts are much more common and that intervention in such cases offers no benefit and may even be harmful. Also, the emotional and financial burden of evaluation, surveillance, and prophylactic surgery should not be underestimated in this decision-making process.[21] Here we review the characteristic features that help identify cyst types, discuss the risk of malignant transformation, and provide an approach to the evaluation and management of pancreatic cysts.

Diagnosis of Pancreatic Cysts

There are more than 20 types of epithelial and nonepithelial pancreatic cysts, but the majority belong to the six most common histologic categories.[22,23] The two most prevalent benign lesions, pseudocysts and serous cystadenomas, account for 15 to 25% of all pancreatic cysts.[24] The two types of mucinous cysts, intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), are the predominant premalignant cystic lesions and account for approximately 50% of cysts that are found incidentally on imaging for other indications. Solid pseudopapillary neoplasms and cystic pancreatic neuroendocrine tumors are two less common malignant cystic neoplasms. Figure 1 provides an overview of the

KEY POINTS

PANCREATIC CYSTS

- Pancreatic cysts are common and are being discovered at an increasing rate on cross-sectional imaging, but only a minority progress to cancer.
- The most important goal is to identify the small percentage of cystic lesions associated with a substantial risk of cancer, and this should be done through a multidisciplinary evaluation based on an algorithmic approach.
- In many cases, imaging, symptom assessment, and laboratory tests can help distinguish benign cysts from those associated with a low, intermediate, or high risk of malignant transformation.
- Endoscopic ultrasonography should be considered for equivocal findings or intermediate-risk cysts.
- Endoscopic ultrasonography and fluid aspiration for cytologic and molecular analysis may help in risk stratification for patients with intermediate-risk cysts.
- Surgical evaluation is warranted for high-risk cysts and for intermediate-risk cysts with multiple risk features, whereas surveillance is used for low-risk cysts.

characteristics of pancreatic cysts and the associated risk of cancer.

Pseudocysts emerge after acute or chronic pancreatitis and typically appear as single or multiple unilocular cysts that may contain debris. Although they are often connected to the pancreatic duct, this may be challenging to confirm. In the absence of antecedent pancreatitis, the diagnosis of a pseudocyst should be made with great caution. A pancreatic cyst identified at the initial presentation of a patient with pancreatitis should raise a red flag, since this cyst could be the cause rather than the consequence of the pancreatitis and should therefore not be considered a pseudocyst. Most pseudocysts resolve spontaneously, and intervention is warranted only for those that are symptomatic.

Serous cystadenomas are benign, slow-growing lesions that predominantly affect women in the fifth to seventh decades of life.[25] These cysts commonly have a microcystic (honeycomb) appearance but may be manifested as solid, macrocystic or unilocular lesions.[26] A central scar on computed tomography (CT) or magnetic resonance imaging (MRI) is a pathognomonic feature, but it is observed in only 30% of cases.[27] In the absence of typical morphologic features, further evaluation may be necessary to confirm the diagnosis. Although most cases are asymptomatic, large serous cystadenomas can cause abdominal pain, pancreatitis, and biliary obstruction.

MCNs are the less common type of mucinous cysts. They characteristically contain ovarian-like stroma and almost exclusively affect women in the fourth to sixth decades of life. MCNs are single, thick-walled, mostly unilocular cysts that are generally situated in the distal pancreas. In contrast to intraductal papillary neoplasms, which are much more common, MCNs have no communication with the pancreatic ducts. Although rare, the presence of peripheral (eggshell) calcifications is a diagnostic hallmark. The risk of advanced neoplasia (high-grade dysplasia or cancer) in patients with MCNs was previously reported to be as high as 30 to 40%, but when the presence of pathognomonic ovarian-type stroma is confirmed, only 5 to 15% of MCNs contain invasive cancer.[28-32]

IPMNs are the most common type of mucinous cystic lesions, with an equal sex distribution and a peak incidence between the fifth and seventh decades of life.[33,34] These neoplasms, which arise from the ductal cells, are often multifocal and located throughout the pancreas. IPMNs are classified according to ductal involvement as main-duct, branch-duct, or mixed-type IPMNs. Main-duct IPMNs, which are less common than the branch-duct and mixed-duct types, are characterized by diffuse or segmental dilatation of the main duct (often due to excessive intraductal mucin production) in the absence of a cystic lesion.[35] On endoscopy, a bulging, mucin-extruding, "fish-mouth papilla" is pathognomonic for main-duct IPMNs. Branch-duct IPMNs can be single or unilocular but often occur in a cluster resembling a bunch of grapes.[36] An estimated 21 to 40% of branch-duct IPMNs are multifocal, with multiple lesions throughout the pancreas. In mixed-type IPMNs, both the main and branch ducts are involved. Although these lesions are usually asymptomatic, a minority of them cause pancreatitis or pain as a result of mucinous ductal

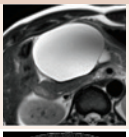
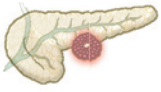
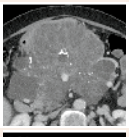
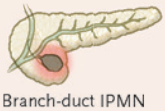
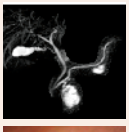
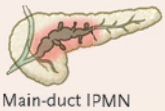
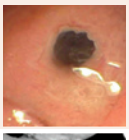
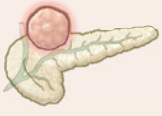
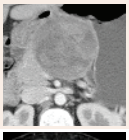
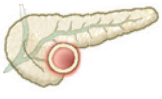
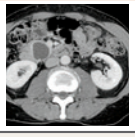
Cyst Type	Patient Characteristics and Clinical Presentation		Imaging Findings		Malignant Potential
Pseudocyst	Associated with antecedent acute or chronic pancreatitis		Unilocular or multilocular May be connected to MPD		0%
SCA	Predominantly in women (60% of cases) Occurs in 5th–7th decades of life Mostly asymptomatic		Microcystic or oligocystic Central scar No communication with pancreatic duct		0%
IPMN	Equal sex distribution Occurs in 5th–7th decades of life Mostly asymptomatic May cause pancreatitis	 Branch-duct IPMN	Communication with pancreatic duct Multiplicity		1–38%
		 Main-duct IPMN	MPD dilatation Fish-mouth papilla		33–85%
MCN	Almost exclusively in women (90% of cases) Occurs in 4th–6th decades of life Mostly asymptomatic		Mostly pancreatic tail Unilocular or oligolocular Thickened wall Eggshell calcifications in 25%		10–34%
SPT	Almost exclusively in women (90% of cases) Occurs in 2nd or 3rd decade of life Mostly asymptomatic		Heterogeneous Eggshell calcifications		10–15%
CNET	Variable age and sex Mostly asymptomatic 10% Are functional		Enhancing, thickened wall		5–10%

Figure 1. Common Types of Pancreatic Cysts and Their Characteristics.

The clinical and imaging characteristics, as well as the risk of malignancy for each of the six most common pancreatic cyst types, are shown. The risk of metastatic disease is shown for SPT and CNET. SCA denotes serous cystadenoma, IPMN intraductal papillary mucinous neoplasm, MCN mucinous cystic neoplasm, SPT solid pseudopapillary tumor, and CNET cystic neuroendocrine tumor.

obstruction. The risk of malignant transformation depends on the histologic and anatomical subtypes and ranges from 1 to 38% for branch-duct IPMNs and 33 to 85% for main-duct or mixed-type IPMNs. These estimates are mostly from surgical series, and more recent data suggest the risk may be lower.[14,37,38] The probable field defect responsible for the multifocality also provides a small concomitant risk of pancreatic cancer, separate from the cyst of interest.[34,37,38]

Two less common cystic lesions, solid pseudopapillary neoplasms and cystic pancreatic endocrine neoplasms, have low but variable metastatic potential[28,39] and distinctive features on imaging. Solid pseudopapillary neoplasms most often develop in women in their second or third decade of life.[40,41] These lesions, which can be located throughout the pancreas, have a well-demarcated, heterogeneous appearance, with both solid and cystic components and, in some cases, irregular calcifications.[42] The majority of solid pseudopapillary neoplasms are associated with a low risk of metastasis, and 10 to 15% are classified on histologic evaluation as solid pseudopapillary carcinoma.[43] Cystic pancreatic endocrine neoplasms arise from the pancreatic endocrine cells and are essentially a cystic degeneration of pancreatic neuroendocrine tumors, often with thick, enhancing walls on radiologic imaging.[44]

Although most of these neoplasms are sporadic and nonfunctioning, up to 10% arise in patients with multiple endocrine neoplasia type 1.[45] More than 80% of cystic pancreatic endocrine neoplasms express somatostatin receptors, which can be detected by means of positron-emission tomography with octreotide or dotatate tracers. Features associated with a poor prognosis, which are similar to those for solid pancreatic endocrine tumors, include a high histologic grade, a diameter of 2 cm or more, symptoms, a Ki-67 proliferation index of 3% or higher, and lymphovascular invasion.[46]

Establishing the cyst type is a crucial first step in the management and subsequent risk assessment of pancreatic cysts. Analysis of imaging features and demographic data results in accurate classification of 70 to 80% of cysts.[2,18] When the diagnosis is equivocal, investigation with endoscopic ultrasonography (possibly with fluid or fine-needle aspiration) may be helpful. Small cysts that lack distinctive features and cannot be characterized (so-called unspecified cysts) are generally presumed to be mucinous and managed accordingly.

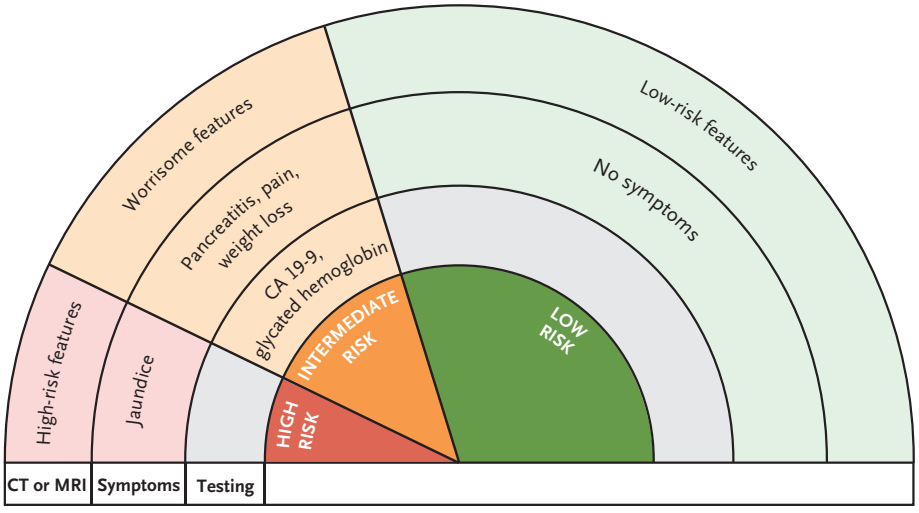
ASSESSMENT OF MALIGNANCY RISK

The presence of a pancreatic cyst often causes unwarranted concern and anxiety about the possibility of cancer. Accurately assessing the risk of malignant transformation remains challenging because of our limited understanding of cyst biology, bias associated with surgical series, and the lack of data from prospective observational studies. The aim is to classify cysts as either benign lesions without malignant potential or lesions associated with a low, intermediate, or high risk of advanced neoplasia (defined as high-grade dysplasia or invasive cancer). In the case of cysts that are unequivocally benign on imaging, such as serous cystadenoma and pseudocysts, further evaluation of the risk of malignant transformation is not needed, and management decisions are primarily based on symptoms related to local effects. Low-risk cysts are those for which there is no risk or only a minimal risk of current advanced neoplasia and a low risk of future malignant progression. These are mostly small, mucinous cysts, predominantly branch-duct IPMNs. Intermediate-risk cysts are associated with a minimal risk of current advanced neoplasia but with a moderate risk of future malignant progression. High-risk cysts are associated with a high probability of current advanced neoplasia. Most intermediate- and high-risk lesions are mucinous cysts, with substantially fewer cases of solid pseudopapillary tumors and solid pancreatic endocrine tumors and rare cases of cystic degeneration of carcinoma.[47]

The initial, noninvasive evaluation of cysts with malignant potential is summarized in Figure 2A. The evaluation starts with a review of imaging features, followed by consideration of relevant symptoms and laboratory tests. Imaging studies should be evaluated first for the presence of high-risk stigmata and other worrisome features. The presence of high-risk stigmata (including biliary obstruction, dilatation of the main pancreatic duct of >10 mm, and a solid enhancing mural nodule of ≥5 mm) has a high positive predictive value for advanced neoplasia, ranging from 56 to 89% (Fig. 3A).[48] Worrisome features, such as a cyst size greater than 3 cm in diameter, main-duct dilatation of 5 to 10 mm, a contrast-enhancing mural nodule of less than 5 mm, an enhancing or thickened cyst wall or septations, lymphadenopathy, a change in the caliber of the pancreatic main duct with distal pancreatic atrophy, and an increase in cyst size greater than 20% or approximately 2.5 mm in diameter per year, are also associated with an increased risk of advanced neoplasia, albeit a lower risk than that associated with the high-risk stigmata (Fig. 3B).[49,50] The absence of these imaging findings is consistent with a low risk of malignant potential.

A subsequent evaluation of symptoms can aid in risk stratification, although a minority of cysts are symptomatic. Jaundice that is caused by biliary obstruction is considered a high-risk feature. Pancreatitis (due to obstruction of the pancreatic duct by the cyst or produced mucin) and abdominal pain are considered intermediate-risk factors when they are related to the cyst, which is often difficult to confirm. With respect to laboratory testing, an elevation in levels of the serum marker CA 19-9 has been associated with an increased risk of malignant transformation.[51,52] Similarly, new-onset diabetes is associated with an increased risk of advanced neoplasia. Therefore, an elevation in CA 19-9 and newly abnormal levels of glycated hemoglobin are both associated with an intermediate risk.[53]

A Approach to the Assessment of Cancer Risk in Patients with Pancreatic Cysts



B Algorithm for the Management of Presumed Mucinous Cystic Lesions

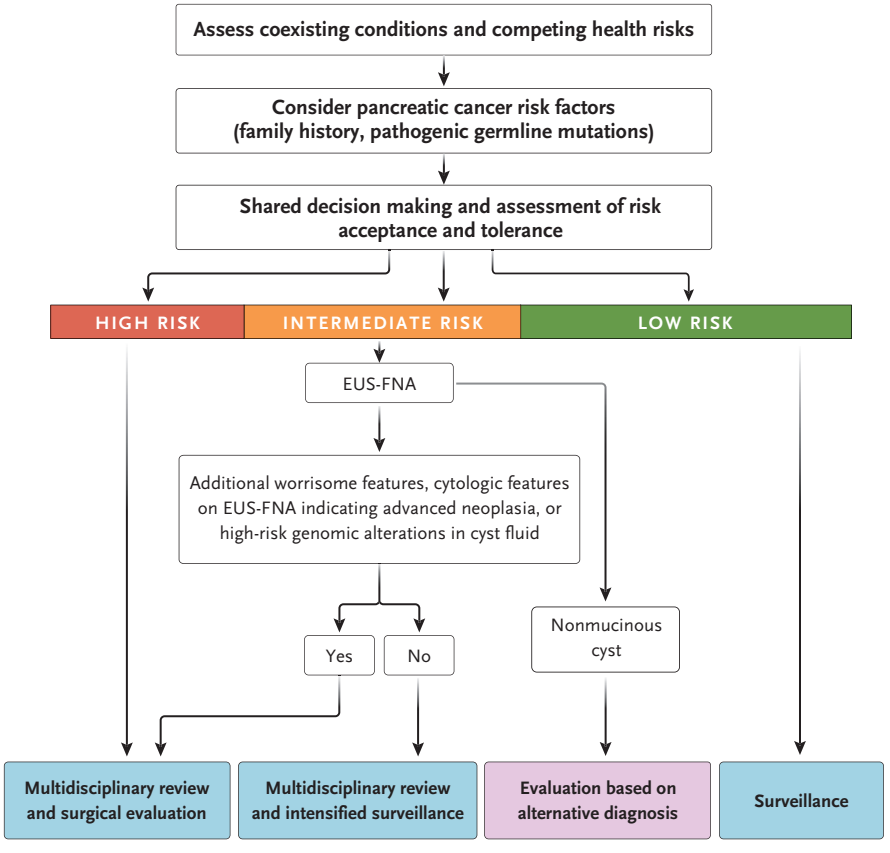


Figure 2 (facing page). Assessment of Cancer Risk and an Algorithm for the Management of Presumed Mucinous Pancreatic Cysts.

Panel A shows the approach to an assessment of the risk of malignant transformation in patients with pancreatic cysts. The first step in risk stratification is an imaging evaluation for the presence of high-risk stigmata or worrisome features. If such stigmata and features are absent, the imaging is thought to indicate a low risk. The second step is a consideration of symptoms, which may be indicative of either a high-risk cyst or a worrisome cyst. Finally, laboratory tests are performed for new-onset diabetes (based on the glycated hemoglobin level) and the level of CA 19-9, with positive results considered to indicate an intermediate risk. The highest risk category in any of the three parts of the evaluation (imaging studies, symptom assessment, and laboratory testing) provides the basis for classifying a newly identified cyst as posing a high, intermediate, or low risk of cancer. Panel B shows an algorithm for the management of cystic lesions that are presumed to be mucinous. Categorization of a cyst according to risk is followed by a consideration of coexisting conditions and competing health risks, as well as risk factors for pancreatic cancer. The next step in the management of the cyst (further evaluation, surgical intervention, or surveillance) is based on shared decision making with the patient, which includes a consideration of the patient's risk tolerance. EUS-FNA denotes endoscopic ultrasound–guided fine-needle aspiration.

Low-risk imaging features and the absence of symptoms and laboratory abnormalities are consistent with a low-risk of malignant transformation.

ENDOSCOPIC EVALUATION OF PANCREATIC CYSTS

In selected cases, a review of noninvasive imaging features is followed by endoscopic ultrasonography (which may serve as a secondary imaging technique).[54] Its primary use is to enhance risk stratification in patients with intermediate-risk cysts. In addition, endoscopic ultrasonography may help to affirm the diagnosis of benign or low-risk cysts. Finally, in patients with high-risk cysts, the patient's preference may justify the use of endoscopic ultrasonography to establish a preoperative diagnosis of suspected advanced neoplasia.

As compared with MRI, endoscopic imaging has a slightly higher accuracy for identifying ductal communication, has a higher sensitivity for detecting small mural nodules, and can be used to identify the pathognomonic fish-mouth papilla.[55] Contrast-enhanced endoscopic ultrasonography has become a particularly valuable imaging technique for confirming the presence of epithelial nodules, which is probably the strongest predictive risk factor for malignant transformation, aside from main-duct dilatation (Fig. 3B).[56] When a solid component is identified, this is the area to target for fine-needle aspiration. Alternatively, an intracystic biopsy specimen may be obtained with microforceps, which is passed through an endoscopic ultrasound–guided needle, although this carries a small risk of pancreatitis and bleeding.[57]

Fine-needle aspiration of cyst fluid is considered to be a safe procedure. The majority of cysts contain only fluid, and the yield for obtaining a cytologic diagnosis is low.[58] Measurement of amylase, carcinoembryonic antigen (CEA), and glucose levels in cyst fluid can aid in establishing the diagnosis but is not helpful in determining the grade of neoplasia (Table 1).[16,59,60] An elevated amylase level suggests communication with the pancreatic ductal system and is characteristic of pseudocysts and IPMNs. Conversely, a very low level of amylase in cyst fluid essentially rules out a pseudocyst. CEA levels exceeding 192 ng per milliliter are seen in 75% of mucinous cysts, and very low levels almost rule them out. However, the level of CEA in cyst fluid does not correlate with the risk of advanced neoplasia. In addition, a low level of glucose in cyst fluid (<50 to 80 ng per milliliter) has been shown to be 90 to 94% accurate in distinguishing mucinous from nonmucinous cysts.[61,62]

DNA can be isolated from cyst fluid, and the detection of mutations associated with specific neoplasms can be helpful, particularly when other findings are inconclusive and the amount of fluid obtained is small (≤0.5 ml).[63] The presence of a *VHL* mutation is nearly 100% specific for serous cystadenoma but is identified in only 25 to 50% of cases.[64,65] The *KRAS* mutation, which is considered a founder mutation, is more than 95% specific for either type of mucinous cyst, with a sensitivity of 60 to 70%. Mutations in *GNAS* are specific for IPMNs (but not MCNs)

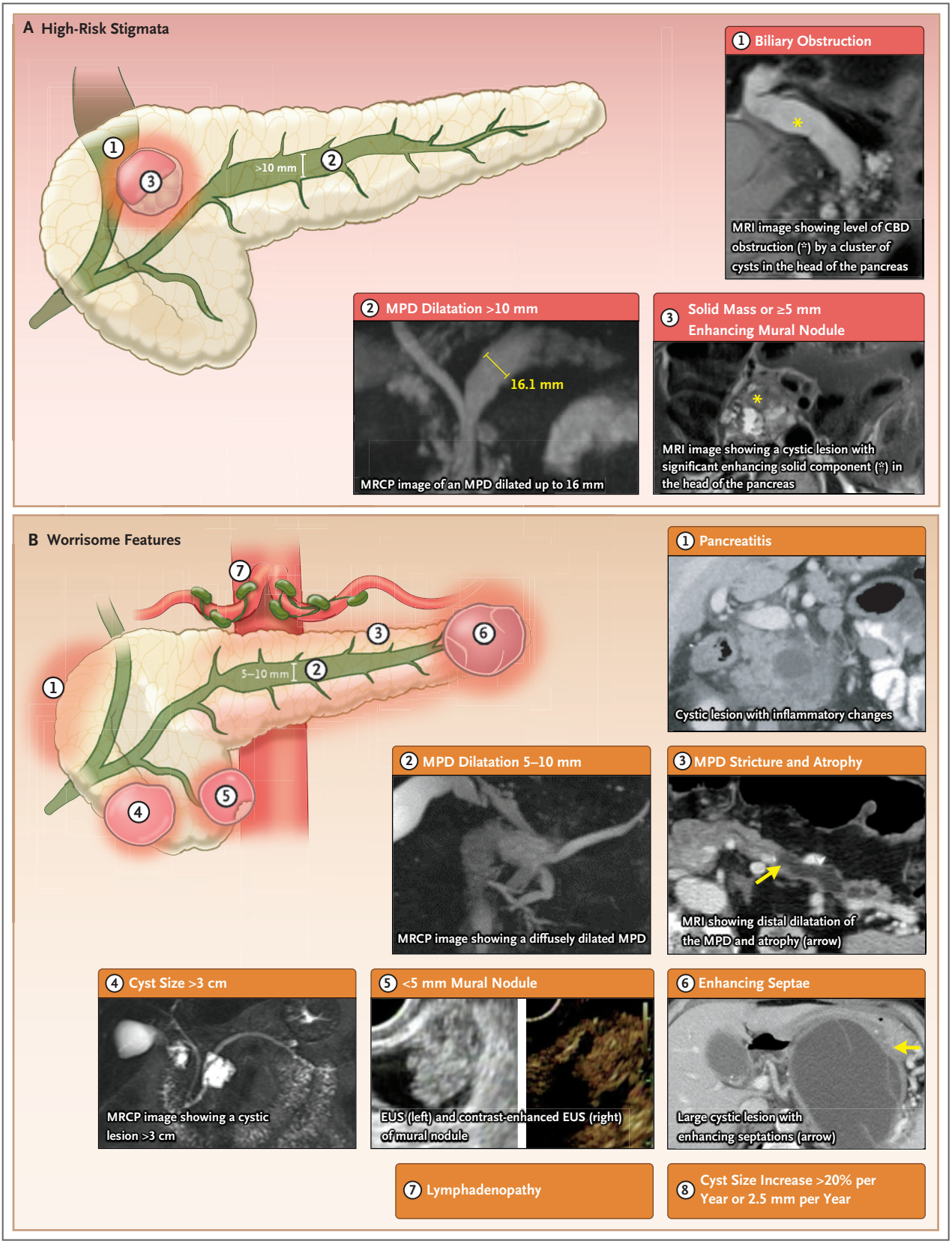


Figure 3 (facing page). Characteristic High-Risk Stigmata and Worrisome Features on Imaging Studies.

Panel A shows characteristic high-risk stigmata on imaging studies, including biliary obstruction, main pancreatic duct (MPD) dilatation exceeding 10 mm, and a solid mass or enhancing nodule that is 5 mm or more in diameter. Panel B shows characteristic worrisome features: pancreatitis, cysts that are larger than 3 cm in diameter, an enhancing mural nodule that is less than 5 mm in diameter (as shown on contrast-enhanced endoscopic ultrasonography), an obstruction of the main pancreatic duct with 5 to 10 mm of dilatation, enhancing septations, and lymphadenopathy. Among patients who have undergone previous imaging, a growth rate exceeding 20% or 2.5 mm per year is considered to be worrisome. CBD denotes common bile duct, and MRCP magnetic resonance cholangiopancreatography.

and are detected in 30 to 60% of cases. The absence of a *VHL* mutation combined with the presence of a *KRAS* or *GNAS* mutation is nearly 100% specific for mucinous cysts, with an accuracy of 97%.[62] Detection of a *CTNNB1* mutation has high specificity for solid pseudopapillary tumors, and the presence of a *MEN1* mutation has high specificity for cystic pancreatic endocrine neoplasms.

Mutational status can also provide information about the risk of advanced neoplasia, especially in the absence of cytologic abnormalities. Genetic abnormalities in oncogenes and tumor suppressor genes such as *TP53*, *CDKN2A*, *SMAD4*, and *CTNNB1* and in genes involved in the mammalian target of rapamycin (mTOR) pathway (*PIK3CA*, *PTEN*, and *AKT1*) are most commonly found in mucinous cysts with high-grade dysplasia or cancer.[65,66] These genomic alterations aid mostly in risk stratification for intermediate-risk cysts.[67] Current data and recent clinical practice guidelines increasingly support the integration of DNA-based mutational testing in the diagnostic evaluation of pancreatic cysts.[14]

MANAGEMENT OF MUCINOUS AND PRESUMABLY MUCINOUS CYSTS

After a definitive or presumptive diagnosis of a mucinous cyst has been made, the appropriate approach to management may be surgical intervention, watchful waiting and surveillance, or refraining from further action. In the process of selecting a management plan, various factors need to be considered, including the estimated risk of malignant transformation, the patient's overall health, and their other risk factors for pancreatic cancer. Before initiating additional diagnostic evaluation, it is crucial to identify any underlying risk factors for pancreatic cancer. Such factors include a family history of the disease and specific germline variants, along with environmental and host factors. Next, coexisting conditions and competing health risks should be taken into account. Finally, in the process of shared decision making, the patient's preferences and risk tolerance need to be considered (Fig. 2B).[68]

Most guidelines recommend that patients with high-risk cysts and an acceptable operative risk undergo surgical resection without further evaluation. For main-duct or mixed-duct IPMNs, localizing the at-risk portion of the pancreas on cross-sectional imaging may be difficult, and preoperative or intraoperative pancreatoscopy can help establish the ductal margins.[69] Minimally invasive surgical approaches are increasingly being used in these cases. In centers with experience in such approaches, the outcomes are similar or superior to those with open surgery, and the recovery time and length of hospital stay are shorter.[70]

The decision-making process is most complex for intermediate-risk cysts, the majority of which are or are presumed to be mucinous. Endoscopic ultrasonography and cyst-fluid analysis can be particularly helpful in these cases.[28] The presence of multiple or additional worrisome features, cytologic features indicating advanced neoplasia, or high-risk genomic alterations in cyst fluid favors surgical resection, whereas their absence justifies intensified surveillance. Although IPMNs are often multifocal, the associated cancer risk correlates with the highest-risk cysts; hence, segmental resection of the affected part of the gland is usually pursued.[36] After resection of an IPMN, continued surveillance of the remaining gland is required even in the absence of cancer, given the multifocality of the disease.

In some instances, even low-risk cysts are resected. A typical example is a mucinous cystic neoplasm, which generally occurs in healthy women in middle age, and the required surgical resection limited to a distal pancreatectomy. Although the risk of advanced neoplasia is very low for lesions that are less than 4 cm in diameter, resection is often performed, since the negligible risk of postoperative recurrence makes further surveillance redundant.[69]

Table 1. Cyst-Fluid Characteristics and Genes Altered in Common Types of Pancreatic Cysts.*

Cyst Type	Macroscopic and Cytologic Features	CEA Level	Glucose Level	Amylase Level	Altered Genes	
					Associated with Cyst Type	Associated with Advanced Neoplasia
Pseudocyst	Macrophages and lymphocytes, debris	Variable	High	High	None	None
SCA	Proteinaceous debris and blood, glycogen-rich cuboidal epithelial cells	Very low	High	Low	*VHL*	None
IPMN	Thick mucinous fluid, mucinous epithelial cells, papillary structures†	High	Low	High	*KRAS*, *GNAS*	*TP53*, *CTNNB1*, *CDKN2A*, *SMAD4*, genes involved in mTOR pathway‡
MCN	Thick mucinous fluid, mucinous epithelial cells, ovarian-type stroma†	High	Low	Low	*KRAS*	*TP53*, *CDKN2A*, *CTNNB1*, *SMAD4*, genes involved in mTOR pathway‡
SPT	Hemorrhagic debris; monomorphic, discohesive small cells; hyaline globules and grooved nuclei	Variable	Normal	Low	*CTNNB1*	None
CNET	Uniform cells in loosely cohesive clusters; coarse, granular, chromatin-containing nuclei	Variable	Normal	Low	*MEN1*	None

* CEA denotes carcinoembryonic antigen, CNET cystic neuroendocrine tumor, SCA serous cystadenoma, and SPT solid pseudopapillary tumor.
† Ovarian stroma in mucinous cystic neoplasms (MCNs) and papillary structures in intraductal papillary mucinous neoplasms (IPMNs) are histologic findings that are observed only in rare cases in samples obtained by means of fine-needle aspiration or microforceps biopsy.
‡ Genes involved in the mammalian target of rapamycin (mTOR) pathway include *PIK3CA*, *PTEN*, and *AKT1*.

For most low-risk cysts, surveillance is recommended, with its intensity depending on the baseline risk. Follow-up every 6 months is advised in the first year, with yearly follow-up thereafter, but the interval can be lengthened with continued stability of the lesion. Surveillance is typically performed with cross-sectional imaging (preferably MRI with magnetic resonance cholangiopancreatography or, if that is unfeasible, with contrast-enhanced CT) or, for larger cysts and cysts with worrisome features, MRI and endoscopic ultrasonography on an alternating schedule or combined. It is increasingly possible to perform focused imaging studies, such as limited MRI of the pancreas, which may offer faster and less expensive surveillance. Measurement of CA 19-9 values and monitoring for the development of diabetes or rapidly increasing glycated hemoglobin levels are adjuncts in surveillance (Fig. 4). Cyst stability is typically defined as less than a 20% increase in the greatest diameter or growth of less than 2.5 mm per year. Faster growth or the development of new intermediate-risk or high-risk features should warrant reconsideration of endoscopic ultrasonography, with or without guided fine-needle aspiration or biopsy, or surgical resection.

Current data do not unequivocally support discontinuing surveillance. However, for low-risk lesions that have remained stable for years, the risk of progression is minimal, and cessation of surveillance becomes a reasonable option.[37,71] Also, a patient's health status needs to be reevaluated regularly, since a change in health status may warrant adjustment of surveillance goals.[72]

CONCLUSIONS AND FUTURE PERSPECTIVES

Pancreatic cysts are strikingly common, mostly incidental findings. Although the majority of these cysts are associated with a very low risk of malignant transformation, a minority may offer an opportunity to recognize and eliminate high-risk precursors of pancreatic cancer. Several guidelines provide recommendations for evaluation, treatment, and surveillance, but they are based on expert opinion rather than solid evidence. Fortunately, an initiative to develop a unified global guideline in the next 1 to 2 years is widely endorsed.

Cyst Size and Features	Year 1	Years 2–5	After >5 Years of Stability
<1 cm without worrisome features or high-risk stigmata	**12 Months** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels **Or consider** • Ceasing surveillance
1–2 cm without worrisome features or high-risk stigmata	**6–12 Months** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 1–2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels **Or consider** • Ceasing surveillance
2–3 cm without worrisome features or high-risk stigmata	**Alternating every 6 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Either in 6–12 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Every year** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels • Continue surveillance
>3 cm or worrisome features (when surgical resection is not pursued)	**Alternating every 3 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Alternating every 3–6 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 6–12 months** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels • Continue surveillance

Figure 4. Surveillance Approaches According to the Size and Features of Mucinous Cysts.

Surveillance approaches are informed by baseline findings in cysts that are presumed to be mucinous. When continued surveillance is chosen, the frequency and approaches used depend on the baseline risk.

An important goal in the management of pancreatic cysts is to reduce the surveillance burden for low-risk lesions while improving the recognition of malignant and premalignant cysts. To accomplish this, prospective studies are needed to determine the true predictive value of known risk factors for cancer. Also, advances in our understanding of the molecular evolution of cystic precursors will lead to the identification of increasingly sensitive biomarkers derived from either cyst fluid, pancreatic juice, or blood. The integration of radiomics (machine learning and artificial intelligence) and advances in endoscopic imaging, such as needle-based, intracystic confocal microscopy, may enhance the sensitivity of risk stratification.[73,74] Although surgery has become much safer, alternative and less invasive techniques are needed, especially for prophylactic interventions. Endoscopic ultrasound–guided pancreatic cyst ablation may be such an option. Early experience with injection of cytotoxic agents or endoscopic ultrasound–guided radiofrequency ablation have shown promise, but randomized trials are needed to define their clinical usefulness.[75-77]

The current approach to management relies on identifying the cyst type and conducting a multimodal assessment of the risk of cancer, an assessment that is mostly noninvasive, with selective use of endoscopic ultrasonography and tissue sampling. The best personalized approach will be provided by models that combine risk factors, clinical variables, imaging characteristics, and molecular markers.[47,78] Treatment and surveillance decisions should follow an algorithmic framework that is overseen by a multidisciplinary team and that incorporates shared decision making with the patient.

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