Diagnostic Dilemma

Pancreas Cancer vs Chronic Pancreatitis

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KEYWORDS

• Chronic pancreatitis • Pancreatic ductal adenocarcinoma • Pancreatic cancer
• Groove pancreatitis • Mass-forming pancreatitis • Diagnostic dilemma

KEY POINTS

- Chronic pancreatitis and pancreatic cancer can present with signs and symptoms of abdominal pain, obstructive jaundice, and/or weight loss. When chronic pancreatitis is mass-forming, affects the duodeno-pancreatic groove, and/or when biopsies are inconclusive, management is especially challenging.
- Computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) are noninvasive imaging modalities permitting visualization of pancreatic parenchyma. Secretin-stimulated MRCP may enhance diagnostic accuracy.
- Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) visualize the pancreatic ductal architecture and enable tissue sampling. ERCP offers diagnostic and therapeutic interventions for ductal strictures and biliary obstructions.
- Carbohydrate antigen 19-9 and CEA aid in diagnosing pancreatic ductal adenocarcinoma, assessing metastasis risk, and monitoring treatment response or recurrence. Interpretation requires correlation with imaging and clinical findings.
- In chronic pancreatitis with pancreatic head involvement, failed medical management, and malignancy concern, pancreatoduodenectomy is preferred over drainage procedures.

INTRODUCTION

Distinguishing chronic pancreatitis (CP) from pancreatic ductal adenocarcinoma (PDAC) is challenging and leads to severe consequences for patients if misdiagnosed. Patients may present with indistinguishable symptoms of weight loss and obstructive jaundice. There are also overlapping risk factors for both diseases, including genetic predisposition, smoking, and alcohol use.[1,2] CP itself is a risk factor for PDAC; there are currently no established guidelines for routine cancer screening in patients with

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Surg Oncol Clin N Am 35 (2026) 1–15
https://doi.org/10.1016/j.soc.2025.05.004 **surgonc.theclinics.com**

Abbreviations	
CP	chronic pancreatitis
PDAC	pancreatic ductal adenocarcinoma
CT	computed tomography
MRCP	magnetic resonance cholangiopancreatography
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopy ultrasound
FNA	fine-needle aspiration
FNB	fine-needle biopsy
CEA	carcinoembryonic antigen
DM	diabetes mellitus
CBD	common bile duct
CA 19-9	Carbohydrate antigen 19-9
USPSTF	US Preventive Services Task Force

a history of CP, though guidelines do exist for patients with other high-risk features that may predispose them to develop PDAC. In most cases of CP, pancreatic ductal obstruction is caused by edema and fibrosis. However, when patients have mass-forming CP, the diagnosis can be more challenging to make and biopsies may help to differentiate between benign and malignant diseases.[3] Additionally, for patients with groove pancreatitis, chronic inflammation is even harder to discern from malignancy.[4,5] False negative biopsies and sampling errors are also possible, and so a negative or nondiagnostic tissue sample must be considered in context of the level of concern for malignancy by clinical and radiographic features.

Misdiagnosis, by imaging, of mass-forming CP as pancreatic adenocarcinoma has been reported in up to 25% of cases,[6] while misclassification of PDAC as CP has been reported in approximately 5% of cases, leading to a treatment delay of over 2 months.[7] Such misclassification can lead to inappropriate management, either by exposing patients with a presumed cancer diagnosis to a major resective surgery with significant potential morbidity or by delaying necessary oncologic treatment. This delay increases the risk of disease progression, potentially compromising curative treatment options if the cancer advances during nononcologic management of presumed CP.

In general, patients diagnosed with PDAC have a 5-year survival rate of approximately 10% to 12.8%,[8–10] although prognosis depends upon how advanced the disease is at the time of diagnosis. For example, patients with locally advanced, unresectable disease at the time of diagnosis have a median survival of 11 months.[11] In comparison, the 5-year survival rate for CP has been reported to be 59% to 80%.[12] This article aims to compare and contrast clinical and diagnostic features of CP and PDAC and summarize current recommendations for management when the diagnosis remains uncertain.

CLINICAL PRESENTATION

Chronic Pancreatitis

CP classically manifests as epigastric pain that may be episodic or chronic, particularly in cases where the etiology is alcohol-related.[13] Associated symptoms may include nausea, vomiting, and anorexia. The average age at diagnosis of CP is 35 to 55 years.[14] Over time, acinar destruction from chronic inflammation may lead to the development of steatorrhea, weight loss, and fat-soluble vitamin deficiencies due to exocrine insufficiency.[15] Patients may develop diabetes due to the destruction of beta cells as the disease progresses. Unlike acute pancreatitis, serum amylase and lipase are typically within normal limits. Patients may exhibit elevated bilirubin and alkaline phosphatase levels due to bile duct compression or stricture related to intrapancreatic edema or fibrosis.

Pancreatic Ductal Adenocarcinoma

PDAC may also present with symptoms of epigastric pain (80% of patients), jaundice, and weight loss.[16,17] Patients are most often diagnosed with PDAC between the ages of 60 to 80.[18] Weight loss may be secondary to impaired exocrine function, and also cancer-related elevations in tumor necrosis factor-alpha. Patients with tumors in the head of the pancreas may also present with symptoms of obstructive jaundice due to mass effects.[19,20] Diabetes mellitus (DM) and obesity are also considered to be associated with the development of PDAC. Patients with a long history of DM are more likely than the general population to develop PDAC; however, an adult patient over the age of 50 with a new diagnosis of DM has an 8-fold higher risk of having PDAC.[21,22]

RISK FACTORS

Among middle-aged men, CP is mostly due to alcohol, while idiopathic causes are more common in women and older adults. Genetic conditions like cystic fibrosis and autoimmune pancreatitis may also lead to CP.[23] Alcohol use precedes CP in 55% to 80% of cases,[23] with 25 to 50 g daily increasing risk by 1.5 times and smoking 15 to 25 cigarettes daily doubling the risk.[24] Recurrent pancreatitis and chronic ductal obstruction from malignancy, fibrosis, gallstones, or strictures can also cause CP.[25]

Genetic and autoimmune factors increase CP risk, with mutations in PRSS1, CFTR, SPINK1, CTRC, CPA1, and CEL playing roles. In contrast, PDAC risk factors include smoking, obesity, high intake of saturated fats or red meat, CP, and genetic mutations such as BRCA, ATM, PALB2, CDKN2A, and MLH1.[26] A family history of PDAC further raises risk—4.6 times with 1 first-degree relative and 6.4 times with 2.[25] Nearly 90% of PDAC cases involve KRAS activation or mutations in tumor suppressor genes like p16/CDKN2A, TP53, and SMAD4.[27,28] Smoking accounts for 11% to 32% of cases, increasing risk 1.7 to 2 times in current smokers and 1.2 times in former smokers,[28–30] with cystic fibrosis and premalignant lesions (eg, intraductal papillary mucinous neoplasm, mucinous cystic neoplasms) also contributing.[31]

CURRENT CONTROVERSIES

When evaluating patients with nonspecific symptoms such as epigastric or back pain, nausea, vomiting, and unintended weight loss—especially in the presence of risk factors such as smoking, alcohol use, or genetic predisposition—the first step should be to take a thorough history focusing on history of familial cancers, risk-factors, recent diabetes diagnosis, weight loss, and steatorrhea. Subsequently, perform a physical examination assessing signs of malnutrition/weight loss, jaundice, and abdominal findings. Additional evaluations include bloodwork such as a complete blood count, a comprehensive metabolic panel including liver function tests, serum amylase, lipase, serum biomarkers such as carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), as well as cross-sectional imaging.[32]

If history, examination, time-course of symptom development, imaging, and biomarkers are insufficient to differentiate between the 2 pathologies, more invasive diagnostic techniques such as endoscopic retrograde cholangiopancreatography (ERCP) or endoscopy ultrasound (EUS) may be warranted.

The initial management of CP and PDAC varies substantially when a definitive diagnosis has been established. Initial management of CP involves symptom management with lifestyle modification such as smoking cessation and alcohol abstinence, whereas, for PDAC, initial management depends upon the stage of the disease. Patients with

PDAC require timely multidisciplinary evaluation to determine the treatment plan and initiate cancer-directed therapy in an expeditious manner.

If symptoms associated with CP significantly impair a patient's quality of life and remain uncontrolled despite lifestyle modifications, optimal pharmacologic pain management, nutritional supplementation, and endoscopic interventions, surgery may be considered for symptom relief.[15] Even though surgery is typically offered after other interventions have been exhausted, particular cases benefit from earlier surgical intervention. One advantage of early surgery is improved pain control when surgery is performed within 3 years of the initial diagnosis.[33,34]

Patients undergoing surgical management of CP may be considered for drainage or pancreas-preserving operations such as the Puestow, Beger, Frey, or Berne procedures, or formal resections, including pancreatoduodenectomy or distal pancreatectomy.[15,24] However, if there is a reasonable concern for PDAC in the differential diagnosis, then such patients should be considered for resection rather than drainage procedures.

This diagnostic approach is outlined in **Fig. 1**, which illustrates the recommended workflow for distinguishing CP from PDAC, in patients without genetic predisposition (**Fig. 1**).

ASSESSMENT AND EVALUATION

The Role of Imaging and Interventional Gastrointestinal Procedures

Computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), ERCP, and EUS are useful in differentiating CP and PDAC. CT and MRCP allow noninvasive visualization of the pancreatic parenchyma and contextualize the pancreas within the anatomy of the entire abdomen to rule out other intraabdominal pathologies and/or metastatic disease. ERCP and EUS allow for tissue sampling. Compared to other modalities, ERCP best visualizes the ductal architecture but it is an invasive procedure requiring anesthesia and associated with risks, such as post-ERCP pancreatitis or duodenal perforation.

Some features may be seen on multiple imaging modalities that should heighten awareness that a patient may have PDAC over or in addition to CP. The *double duct sign* refers to the simultaneous dilation of both the common bile duct (CBD) and pancreatic duct, often with an abrupt distal cut-off point suggestive of a mass; this sign can be seen in CT, MRCP, ERCP, and EUS.[35,36] While often associated with pancreatic malignancy, narrowing and subsequent upstream dilation of both ducts can also occur due to CP or any process causing ampullary stenosis.

The *duct penetrating sign*, best seen on ERCP and MRCP, refers to a smooth, gradual narrowing of the main pancreatic duct as it passes through a mass without overt obstruction. Though this can be seen in early PDAC, it is more often associated with CP as the pancreatic duct traverses a compressible, inflammatory mass.[37,38]

Pancreatic calcifications are associated with alcohol abuse and inflammation,[39] whereas ductal obstruction caused by PDAC characteristically does not include calcifications except in cases where a patient has a history of CP and then develops PDAC. However, the dispersal and displacement of calcifications over time may hint that a tumor is having a mass effect on surrounding tissue. The most sensitive and gold-standard imaging modality to detect calcifications is a CT scan, though calcifications may be seen on MRI and ultrasound.[40,41] Concern for vascular invasion or destruction should raise concern for a malignant process.[42]

Computed tomography

A pancreas protocol CT is a triphasic scan (arterial, venous, portal venous) with thin slices of the pancreas. In the arterial phase (35–40 seconds postcontrast injection),[43]

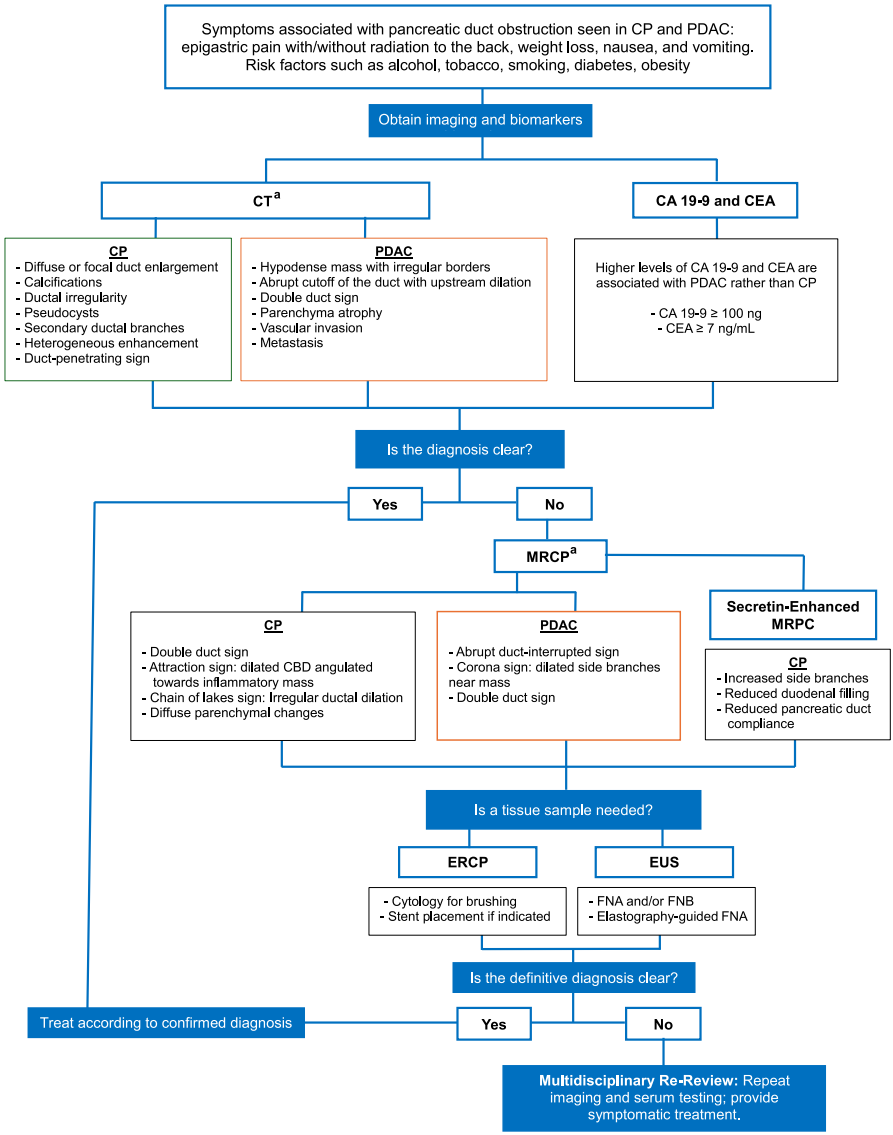

Fig. 1. Diagnostic flowchart differentiating CP from PDAC in patients without genetic predisposition. [a]Classic features of each condition are listed below; while these features may appear in either diagnosis, they are more commonly associated with the condition specified.

subtle differences can be seen in the attenuation of normal parenchyma compared to tumors. Lesions with increased vascularity (eg, neuroendocrine tumors) can be discerned from typically hypoattenuating tumors, such as PDAC. Additionally, vascular invasion can be evaluated. The portal venous phase allows assessment for hepatic metastases, portal vein involvement, and thrombosis[44] (**Fig. 2**A–C).

Specific CT characteristics more commonly associated with CP are diffuse parenchymal changes (eg, atrophy) and the presence of intraductal and parenchymal calcifications.[45] CT is the most sensitive imaging modality to detect pancreatic

calcifications.[43,44] Additionally, the pattern of ductal dilation can help distinguish malignant from benign causes. An abrupt area of dilation suggests malignancy, whereas a smooth narrowing indicates a more compressible, inflammatory focus, like CP. Additionally, an irregular duct with alternating segments of dilation, stricture, and distortion is more indicative of CP (chain-of-lakes appearance).[45] These ductal findings may also be seen on MRCP and/or ERCP.

Magnetic resonance cholangiopancreatography

In CP, parenchymal changes on MRCP include pancreatic atrophy, a depressed T1-weighted signal intensity, and heterogeneous parenchymal texture.[3,46] The pancreatic head or body may show irregular contours, while delayed enhancement with gadolinium contrast reflects chronic inflammation and fibrosis.[1,46] Ductal abnormalities such as the double duct sign, duct penetrating sign, and the chain of lake appearance may also be useful to discern CP from PDAC.[1,47] Specialized MRCP techniques, such as secretin-stimulated imaging, can further aid diagnosis by revealing reduced duodenal filling and decreased pancreatic duct caliber change, indicative of exocrine dysfunction.[46,48] This approach can be especially useful when the diagnosis of CP is in question.

While pancreas protocol CT is commonly used for staging PDAC, MRCP is a viable alternative in centers with expertise in this area. Chen and colleagues describe that MRI-MRCP provides comparable accuracy to CT in the preoperative evaluation and staging of pancreatic tumors. Specifically, they found that there was no significant difference between assessing vascular involvement, tumor resectability, nodal status, or metastasis when choosing one cross-sectional modality over the other.[49]

Endoscopic ultrasound

Endoscopic Ultrasound (EUS) permits evaluation of the pancreatic ducts and parenchyma, aiding in the diagnosis of CP and PDAC. EUS is the most sensitive imaging modality for detecting small lesions less than 3 cm.[50] For CP, the American Pancreatic Association has established specific EUS diagnostic criteria. During the examination, at least 3 typical EUS findings are required to make the diagnosis of CP,[1] including hyperechoic foci and strands, hyperechoic duct walls, parenchymal calcifications, irregular hyperechoic ducts, dilated secondary branches, and pancreatic duct stones.[1,51]

EUS can incorporate elastography, which distinguishes benign from malignant pancreatic masses with 92.3% sensitivity and 80% specificity[8,44] It measures tissue strain and presents a color-coded analysis.[33,46] Scales based on color patterns

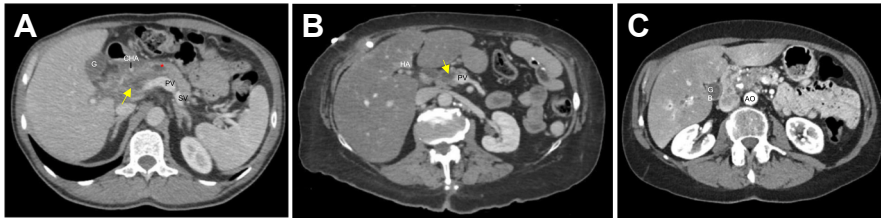

Fig. 2. Examples of pancreas protocol CT scans of challenging diagnostic cases. (*A*) CP (mass-forming) at the head of the pancreas (*yellow arrow*) with main pancreatic duct dilation (*asterisk*); (*B*) PDAC in the head of the pancreas (*yellow arrow*) surrounding the portal vein; (*C*) CP and PDAC at the head of the pancreas with multiple calcifications and an irregular main pancreatic duct. AO, aorta; CHA, common hepatic artery; GB, gallbladder; HA, hepatic artery; PV, portal vein; SV, splenic vein.

have been developed. For example, the scoring system proposed by Giovannini and colleagues ranges from 1 to 5, with higher scores indicating greater tissue heterogeneity, fibrosis, and necrosis—a score of 3 or higher suggests malignancy.[44] However, elastography may not reliably differentiate between CP and PDAC as both may exhibit a similar fibrous structure.[47]

EUS plays a crucial role in obtaining tissue samples through fine-needle aspiration (FNA) and fine-needle biopsy (FNB). When elastography is used alongside FNA to target areas appearing malignant, diagnostic accuracy improves significantly.[52] However, in cases of CP, the extensive fibrosis can resemble malignancy, reducing the accuracy of FNA compared to sampling in normal pancreatic parenchyma.[53] Despite the challenges in distinguishing between CP and PDAC using EUS, obtaining a tissue sample remains the most reliable diagnostic method. A meta-analysis of 16 studies evaluating the use of EUS-FNB to differentiate benign from malignant pancreatic masses reported a sensitivity of 84% and a pooled specificity of 99%.[54] In terms of guiding clinical decision-making, this is most helpful when the FNA/FNB confirms the presence of malignancy, as a negative result does not eliminate concern for malignancy entirely.

Endoscopic retrograde cholangiopancreatography

ERCP serves as a diagnostic and therapeutic tool in distinguishing CP and PDAC. In CP, ERCP has a sensitivity of 82% and specificity of 94% for the diagnosis of CP,[24,55] while in PDAC, the mean sensitivity is 52% and median specificity is 100%.[56] Moreover, ERCP allows brush cytology, which helps identify the presence of malignant cells.[57] A limitation of ERCP is that it only evaluates the duct itself, restricting assessment of the pancreatic parenchyma. This poses a challenge when evaluating deeper fibrotic or malignant masses, regardless of the etiology.[24]

In distinguishing CP and PDAC, ERCP may aid in diagnosis through cytology and through demonstrating the characteristics of the biliary obstruction, whether more consistent with CP or PDAC. In both cases, ERCP offers a therapeutic intervention through biliary decompression. This may be definitive palliative management of biliary obstruction in advanced PDAC; it is less often a definitive approach for CP since even metal stents may obstruct over time and because surgery is ultimately more effective than ERCP in terms of durable relief of biliary obstruction and regarding pain management and quality of life metrics in patients with CP.[18]

Biomarkers

Biomarkers are essential for distinguishing CP from PDAC and serve as tools for monitoring treatment response, such as neoadjuvant chemotherapy in PDAC.

Carbohydrate antigen 19-9

CA 19-9 is produced by normal pancreatic and biliary cells and can be overexpressed in both benign and malignant gastrointestinal (GI) disorders.[32] In PDAC, elevated CA 19-9 has about 80% sensitivity and 86% specificity, though false positives may occur in conditions like CP, cholangitis, cirrhosis, and other GI cancers,[52,53,58] particularly with biliary obstruction. Additionally, about 10% of Caucasians lack the Lewis antigen, which can lead to false negatives as they cannot synthesize CA 19-9.[59,60]

In the context of CP, CA 19-9 levels can also be elevated, but typically not to the same degree as in PDAC. The pooled sensitivity and specificity of CA 19-9 for differentiating PDAC from CP are 82% and 81%, respectively, indicating that while elevated CA 19-9 increases suspicion of PDAC, it is not definitive on its own and should be used in conjunction with other clinical findings and diagnostic tools.[61]

Carcinoembryonic antigen

CEA is a glycoprotein that, under normal conditions after birth, should be undetectable in serum. In malignancies, especially of the GI tract, CEA is overproduced, promoting the inhibition of apoptosis and facilitating cell migration and adhesion.[62] CEA can also be produced by biliary ductal cells in response to ductal occlusion, regardless of whether the underlying condition is malignant or inflammatory.[63] While the degree of elevation can help differentiate between CP and PDAC, serum CEA is not exclusively elevated in cancer. Beyond its role in diagnosis, CEA is a valuable tool for assessing the extent of disease and likelihood of metastatic disease in patients with PDAC, particularly when used in conjunction with other imaging findings.[32,63]

Mean CEA levels are generally lower in CP than in PDAC, making them a useful complement to imaging despite no universal threshold. Higher CEA levels are associated with malignancy and more advanced disease stages. Kalser and colleagues reported CP levels averaging 5.3 ± 4 ng/mL (mostly $\leq$5 ng/mL), while PDAC levels were 10 ± 5 ng/mL in nonjaundiced patients and 27 ± 40 ng/mL in those with jaundice.[64] Sharma and colleagues found averages of 18.6 ng/mL in pancreatitis versus 309 ng/mL in PDAC,[65] and Van Manen and colleagues proposed a 7 ng/mL cutoff for PDAC with an 83% positive predictive value.[66]

CEA levels can be even higher in patients with metastatic disease, with a reported mean of 97 ± 194 ng/mL.[64] Overall, CEA levels are generally higher in pancreatic adenocarcinoma than in CP, making it a useful biomarker for contributing to the distinction between these conditions.[64] Additionally, a systematic review and meta-analysis by Meng and colleagues in 2017 highlighted that while CEA alone has moderate sensitivity, its specificity is high, making it a valuable marker when combined with other diagnostic tools like CA f19-9 for pancreatic cancer.[67]

NONPHARMACOLOGIC AND SURGICAL/INTERVENTIONAL TREATMENTS

Endoscopic Management

The American Society for Gastrointestinal Endoscopy recommends that for patients with CP and severe pain with a known obstructed main pancreatic duct, surgery is superior to endoscopic interventions. Thus, surgical consultation should occur before endoscopic management unless patients have contraindications to or prefer less invasive initial approaches.[24,68,69] Compared to surgery, short-term and long-term pain relief and quality of life are higher in patients undergoing surgery to relieve pancreatic obstruction compared to endoscopy, although there are no differences in endocrine function or exocrine function between the 2 options.[70]

When surgery is performed within 3 years of initial symptom onset as opposed to later in the course for patients with CP, there is a greater likelihood of total pain resolution, less narcotic use, improved quality of life, and lower rates of exocrine and endocrine insufficiency without differences in postprocedural complication rates.[33,71,72]

When biliary stents are placed to manage symptoms of obstruction in CP, covered, self-expandable metal stents are typically preferred over plastic due to higher patency rates, less need for reintervention, and superior pain control.[73] Plastic stents may be considered a palliative option in advanced-stage PDAC and short life expectancies. However, similar to CP, patients with PDAC also have reduced rates of complications and less need for subsequent procedures when metal stents are used compared to plastic stents.[74] While stent placement increases risks of infections, wound dehiscence, and fistulae,[75] it remains necessary when surgery isn't immediately feasible.

Surgery

Surgery may be considered for CP patients whose symptoms persist despite nonoperative treatments and interfere with their daily activities or work. For CP primarily affecting the pancreatic head without concern for malignancy, options include the Beger, Frey, Berne, Whipple, or, less commonly, distal pancreatectomy or Puestow. The Beger procedure divides the pancreas at the neck for separate anastomoses of the head and distal remnant but is technically challenging with risk of injuring the superior mesenteric vein/portal vein during the division of the pancreatic neck and does not drain the entire pancreas, which is thus not adequate in the setting of CP-related multiple pancreatic duct strictures. The Frey procedure cores out the head and adds a longitudinal pancreatojejunostomy, avoiding neck division. The Berne modification similarly cores out the head but lacks a full longitudinal anastomosis and is an option for head-focused CP.[25] Puestow involves a longitudinal pancreaticojejunostomy for disease or stones in the neck or distal pancreas without addressing the head.

Drainage procedures do not entail a formal oncologic resection and are not appropriate if concern remains that the patient may have PDAC. Obtaining frozen sections in the operating room prior to formal resection may help distinguish PDAC from CP when the diagnosis remains in question. However, frozen sections have been historically scrutinized for having high false negative rates and low sensitivity. Recent studies have shown that the diagnostic accuracy of frozen sections is now approximately 90%, with a positive predictive value of 100% and a negative predictive value of 50%.[76,77] Thus, intraoperative biopsies can be used to confirm a diagnosis of PDAC but still cannot necessarily rule out a diagnosis of PDAC when it remains a concern.

In cases of CP where there is uncertainty about, or high suspicion for, the presence of an underlying malignancy, a formal oncologic resection is preferred, and the specific oncologic surgical approach (ie, distal pancreatectomy with/without splenectomy vs pancreatoduodenectomy) depends upon anatomic involvement. For example, groove pancreatitis impacts the area between the pancreatic head, distal CBD, and second part of the duodenum—and is notoriously difficult to distinguish from malignancy. A formal resection, in this case, a pancreatoduodenectomy, would be considered the procedure of choice if there is high concern for malignancy.[78] Time course, consideration of stability versus progression over time, radiologic findings, and tumor markers may help to distinguish CP from PDAC in general. Thus, the surgical approach when selecting between different drainage procedures versus formal oncologic resections should reflect the anatomic involvement as well as the level of concern for cancer versus CP.

NATIONAL GUIDELINES

There are currently no universal guidelines for routine cancer screening in patients with a diagnosis of CP in the absence of other genetic risk factors that predispose them to the development of PDAC. However, such patients should be closely monitored by their multidisciplinary team for symptom progression that could indicate ongoing CP versus development of PDAC. This ongoing care typically includes imaging as well, though there are no formal guidelines as to frequency.

EUS and MRI are the primary screening tools for familial and genetic syndromes linked to PDAC. High-risk patients include those with mutations in BRCA-2, STK11 (Peutz-Jeghers), p53 (Li Fraumeni), CKDN2A (familial atypical multiple mole melanoma), and Lynch syndrome genes (MLH-1, MSH-2, MSH-6).[26] Individuals with hereditary pancreatitis (PRSS1, PRSS2), cystic fibrosis, pancreatic lipase deficiencies

(PNLIP, PNLIPRP2), and related mutations are also at increased risk for CP and PDAC,[26,79] and should start screening 20 years after pancreatitis onset or by age 40. CEL, CaSR, CLDN2, Alpha-1-antitrypsin, GGT, ATM, EPCAM, and PALB2 are additional mutations that should also be considered for early screening.[26,79] Screening is advised for patients with a pathogenic germline mutation plus a family history of PDAC in a first-degree or second-degree relative from the same side, as well as for those with at least 1 first-degree relative diagnosed with PDAC even in the absence of a known hereditary cancer syndrome.[80]

NCCN guidelines suggest PDAC screening for people with germline STK11 (30–35 years or 10 years younger than earliest family PDAC), CDKN2A (40 years or 10 years younger than earliest family PDAC), ATM, or BRCA2 (50 years or 10 years younger than earliest family PDAC). Screening should also begin at age 50 or 10 years younger than the earliest family PDAC for patients with identified pathogenic variants in the other susceptibility genes and with a family history of PDAC in at least 1 first or second-degree relative. Screening is suggested to include MRCP with contrast and/or EUS.[32,81,82]

The American College of Gastroenterology suggests annual screening for patients without any known concerning pancreatic lesions beginning at 50 years, or 10 years before the initial age of the youngest diagnosed first-degree relative with pancreatic cancer, as well as at 50 years for known hereditary pancreatic cancer syndromes. Screening should begin at age 40 for patients with either PRSS1 or CKDN2A gene mutations and at the age of 35 for patients with Peutz-Jeghers disease.[81] For patients with these high-risk conditions, as well as with concerning pancreatic lesions, the interval follow-up should be 6 to 12 months for those deemed to be low-risk and within 3 months for high-risk lesions if surgery has not been planned.

The US Preventive Services Task Force (USPSTF) does not recommend routine pancreatic cancer screening for the general population without symptoms. However, screening is advised for individuals at high risk, such as those with familial pancreatic cancer or inherited genetic syndromes. Notably, USPSTF does not recommend screening for asymptomatic individuals, even if they have risk factors like new-onset diabetes, preexisting diabetes, older age, obesity, smoking, or a history of CP. For those at elevated risk, imaging modalities such as CT, MRCP, and EUS are recommended for screening.[83]

RECOMMENDATIONS

If PDAC cannot be excluded after thorough work-up and multidisciplinary review, a lower threshold for oncologic resection is advised for surgical candidates who show imaging progression (eg, ductal dilation, strictures), symptom progression, or who have elevated genetic risk. Comorbidities, care goals, and quality-of-life considerations must guide patient-centered care. Patient comorbidities, goals of care, and the impact of surgical and medical management on patient quality of life should also be assessed to deliver patient-centered care.

SUMMARY

Differentiating CP from PDAC remains a significant clinical challenge due to the overlap in patient risk factors, symptomatology, and often, imaging findings. While CP itself is a recognized risk factor for PDAC, it can also mimic malignancy, particularly in cases of mass-forming CP, leading to a risk of misdiagnosis. Accurate diagnosis is critical to appropriately guide treatment, including cancer-directed therapy initiation when needed. At times, this may include pancreatectomy when PDAC cannot be excluded in the setting of CP.

Advances in imaging modalities, including pancreas-protocol CT, MRCP, and EUS, have improved diagnostic precision by providing distinct patterns of parenchymal and ductal changes associated with CP and PDAC. However, limitations in sensitivity and specificity, along with overlapping features, highlight the importance of multimodal diagnostic approaches. Until novel biomarkers or screening protocols are validated, careful clinical judgment and risk assessment, combined with a multidisciplinary approach to diagnosis and management, remains essential to improving outcomes in these complex and often interrelated conditions.

CLINICS CARE POINTS

- Cross-sectional imaging with CT-pancreas protocol and/or MRI should be the first diagnostic imaging modality to evaluate the pancreatic parenchyma and to evaluate for secondary signs of the diagnosis of malignancy or CP.
- ERCP and EUS are invasive but offer tissue sampling capabilities that may help to distinguish pancreatic cancer from CP.
- Although patients with CP have an elevated risk for pancreatic cancer, screening is not recommended in the absence of other risk features for pancreatic cancer. For patients with specific known risk factors for pancreas cancer (BRCA-2, Peutz-Jeghers, familial atypical multiple mole melanoma syndrome, and Lynch syndrome, and for those with a first-degree relative with pancreas cancer), screening with MRI or EUS is recommended.
- Frozen sections obtained intraoperatively may aid in distinguishing CP from pancreatic cancer. However, frozen sections have a high positive predictive rate and a low negative predictive rate and, therefore, cannot exclude malignancy.
- If a patient with CP is considered for operative intervention, and if there is any concern for malignancy, resection should be preferred over drainage procedures.

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