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The Incidental Pancreatic Cyst: When to Worry About Cancer

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Incidental pancreatic cystic lesions are a common challenge encountered by diagnostic radiologists. Specifically, given the prevalence of benign pancreatic cystic lesions, determining when to recommend aggressive actions such as surgical resection or endoscopic ultrasound with sampling is difficult. In this article, we review the common types of cystic pancreatic lesions including serous cystadenoma, intraductal papillary mucinous neoplasm, and mucinous cystic neoplasm with imaging examples of each. We also discuss high-risk or worrisome imaging features that warrant a referral to a surgeon or endoscopist and provid several examples of these features. These imaging features adhere to the latest guidelines from the International Consensus Guidelines, American Gastroenterological Association (2015), American College of Gastroenterology (2018), American College of Radiology (2010, 2017), and European Guidelines (2013, 2018). Our focused article addresses the imaging dilemma of managing incidental cystic pancreatic lesions, weighing the options between imaging follow-up and aggressive interventions.
Keywords: Pancreatic cyst; Imaging guidelines; Intraductal papillary mucinous neoplasm; Mucinous cystic neoplasm; Serous cystadenoma

INTRODUCTION

Incidental cysts in the pancreas are encountered in approximately 2.4%–13.5% of patients who undergo abdominal imaging for non-pancreatic related indications [1]. These lesions comprise an array of pathologies ranging from benign to carcinoma in situ or invasive carcinoma. A challenge faced by radiologists is that these lesions often have similar imaging appearances, particularly when they are small, as is often the case with the majority of these lesions. Consequently, the management of these lesions poses significant challenges. The objective for the radiologist is to avoid raising the suspicion of a lesion that is likely benign, while confidently identifying lesions at risk for harboring carcinoma in situ or those with invasive carcinoma. This challenge is further complicated by the fact that the only effective cure is surgical resection, which results in substantial morbidity and occasional mortality [1,2]. We aim to address this challenge by considering the current major guidelines from the International Consensus Guidelines, American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), American College of Radiology (ACR), and European Guidelines (EG), and to discuss our approach for managing incidental pancreatic cystic lesions.

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Incidence and Histologic Types

The incidence of incidental cysts in the pancreas has increased over the last two decades, largely attributed to improved cross-sectional imaging techniques, an aging population, increased utilization of imaging, particularly MR, and increased awareness of these lesions [3,4]. Most asymptomatic unilocular lesions less than 2.5 cm in size do not harbor carcinoma in situ and are not invasive. Generally, follow-up imaging of these lesions is prudent and aligns with the major guidelines. However, a subset of lesions exists where imaging reveals features, termed worrisome or high-risk, indicating an elevated risk of carcinoma in situ

or carcinoma [4,5]. Of note, the International Consensus Guideline defines "worrisome features" and "high-risk stigmata" as specific separate criteria. However, for the purpose of this paper which also references other guidelines, we will use the terms interchangeably as general terms. In such cases, an aggressive approach may include endoscopic ultrasound (EUS), EUS with fine-needle aspiration, or surgical resection. Importantly, the majority of asymptomatic incidental lesions will never progress to cancer. A small number of patients need to be followed up because of the low risk of developing carcinoma in situ or elsewhere in the pancreas [6,7].

Several pathological types of pancreatic cystic tumors have been identified [1,4]. Serous cystadenomas generally occur in patients 60 years of age or older and have a slightly increased incidence in female compared to that in male. These lesions have a characteristic sponge-like or honeycomb appearance, which may be apparent on CT and MRI. Moreover, these lesions are more frequently observed in the head of the pancreas. These tumors classically have a centrally located scar and calcifications which are prominent on CT (Fig. 1). Although these lesions may present as large masses and exhibit mass effect on surrounding structures such as the common bile duct or duodenum, they are uniformly benign. During cyst aspiration, the fluid contains glycogen but not mucin. Often, the imaging appearance is diagnostic and no further workup is required [8].

Intraductal papillary mucinous neoplasms (IPMNs) are one of the most frequently encountered pancreatic cysts worldwide. This lesion is more common in males than in females, although geographical variability in the ratio for female exists [9]. These tumors arise from the columnar epithelium of the pancreatic duct or its side branches. Papillary projections may form as a result of cellular proliferation and dysplasia and characteristically produce mucin. If located in the pancreatic duct side branches, it presents as a cystic lesion surrounded by the pancreatic parenchyma. Additionally, the cyst is often associated with a dilated side branch connected to the main pancreatic duct (Fig. 2). Branch duct lesions are typically benign. IPMNs that arise in the main pancreatic duct cause pancreatic duct dilatation due to chronic and progressive packing of the duct with mucin, which may be identified endoscopically as mucin dripping from the ampulla of Vater. Main pancreatic duct lesions are often associated with carcinoma in situ or invasive carcinoma. In certain cases, lesions involve both the side branch and main pancreatic duct, known as mixed type (Fig. 3). The mixed type has an intermediate potential for harboring carcinomas in situ [8,10]. Furthermore, MRI may be useful for defining the association between a cystic lesion and the main duct, particularly MR cholangiopancreatography (MRCP).

Mucinous cystic neoplasms are far more common in females than in males (9:1 female-to-male ratio) and typically manifest during middle age. This lesion often presents as a cystic mass with enhancing septations, loculations,

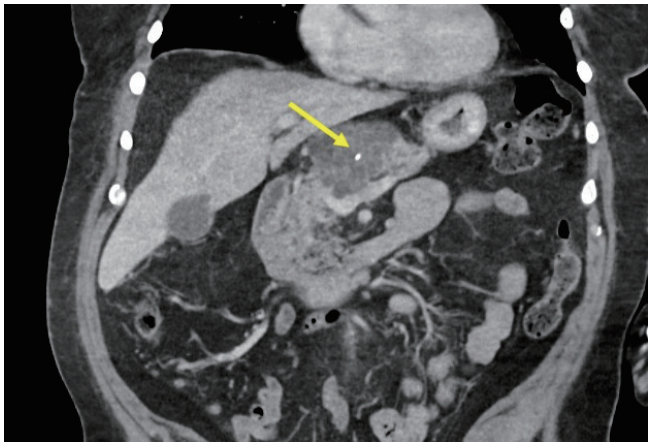

Fig. 1. Coronal portal venous phase contrast-enhanced CT scan of a 66-year-old female demonstrates honeycomb appearance and central calcifications (arrow) of a serous cystadenoma measuring 4.2 cm, located in the pancreatic body. Although not necessary based on imaging criteria, the patient underwent endoscopic ultrasound with fine-needle aspiration yielding benign results.

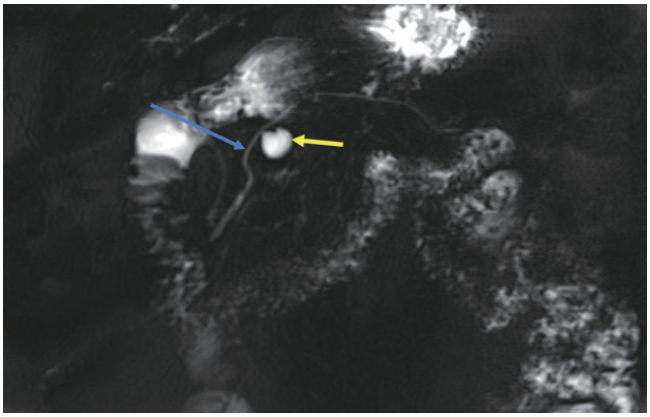

Fig. 2. Coronal heavily T2 weighted MR cholangiopancreatography image of a 75-year-old male demonstrates a cystic lesion (yellow arrow) in the body of the pancreas, connecting to the main pancreatic duct (blue arrow), consistent with branch duct-type intraductal papillary mucinous neoplasm measuring 1.3 cm. Based on imaging, this does not meet the criteria for an endoscopic ultrasound with fine-needle aspiration, thus no pathologic diagnosis has been rendered.

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and mural nodules that represent papillary excrescences, apparent on both MRI and CT (Fig. 4). These lesions tend to present with peripheral calcifications, most notably on CT. On cyst aspiration the cystic fluid contains mucin. The neoplasm may occur in the head or tail of the pancreas, is associated with carcinoma in situ, and is a risk factor for invasive carcinoma. The two cysts that generate mucin, IPMNs and mucinous cystic neoplasms, are associated with malignancy [4,8].

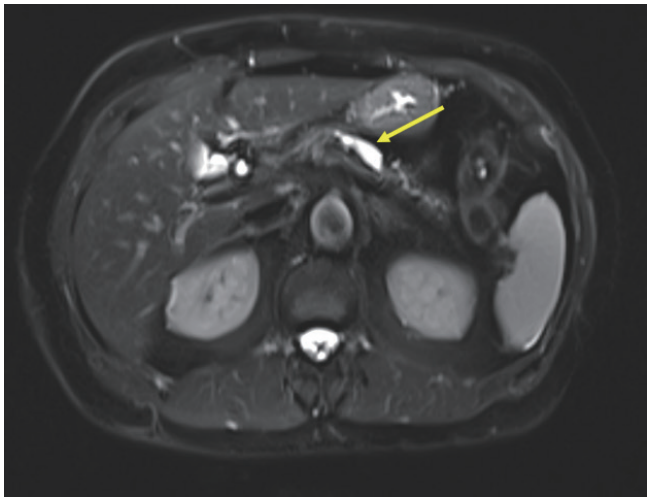

Fig. 3. Axial T2 weighted MRI of a 69-year-old female displays a focally dilated main pancreatic duct in the body/tail measuring 8 mm (arrow). The patient underwent distal pancreatectomy and splenectomy, and pathology is consistent with mixed-type intraductal papillary mucinous neoplasm.

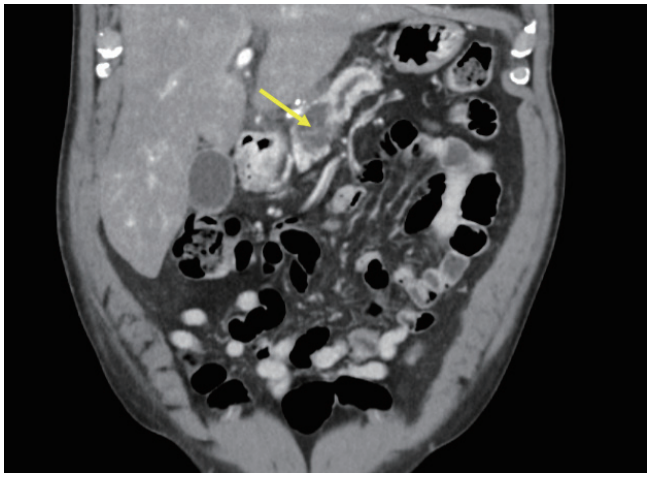

Fig. 4. Coronal, contrast-enhanced CT image in portal venous phase demonstrates a cystic lesion measuring 2.9 cm in the pancreatic neck with thin septations (arrow) and mild pancreatic duct dilation up to 5 mm. The patient is a 71-year-old male who underwent endoscopic ultrasound with fine-needle aspiration based on this imaging. The pathology is consistent with mucinous cystic neoplasm, and no high-grade atypia is identified.

Other cystic pancreatic lesions include pseudocysts, epithelial cysts, lymphoproliferative cysts, and cystic neuroendocrine tumors, which are beyond the scope of this paper [1,4].

Management Guidelines

Currently, the only viable treatment for pancreatic cysts is surgical resection, which is associated with high morbidity and mortality. The low risk of malignant transformation, the high risk of surgical treatment, and the lack of high-quality prospective studies have led to contradictory recommendations for management and surveillance [1]. Numerous guidelines and recommendations have been published outlining surveillance strategies for these lesions [2]. The first guideline was the 2006 International Consensus Guideline (Sendai Guideline), which has been revised twice since then [11-13]. Guidelines have been published for the AGA (2015), ACG (2018), ACR (2010, 2017), and EG (2013, 2018) [1,14-16].

Most guidelines have focused on the identification of high-risk or worrisome features within cystic lesions associated with malignancy [4]. High-risk features included the presence of enhancing mural nodules or solid components, dilatation of the main pancreatic duct (greater than 5 mm), abrupt change in the diameter of the pancreatic duct, cyst size larger than 3–4 cm, interval growth, and positive cytology on fluid aspiration (Table 1). When high-risk features are present, it is recommended that patients be referred to a specialty pancreatic center for further work-up, including EUS, EUS with fine-needle aspiration, or surgical resection. If high-risk features are not present and the patient is willing to undergo surveillance, follow-up imaging is prudent. Patients with advanced age or comorbidities that preclude surgical resection, or those who decline surgical resection, should be excluded from follow-up imaging [1,4].

Notably, the aforementioned guidelines refer to incidentally discovered asymptomatic lesions. If a lesion is associated with symptoms, including pain, obstructive jaundice, or signs suggestive of occult malignancy, such as deep venous thrombosis or unexplained weight loss, an aggressive approach including EUS with fine-needle aspiration or surgical resection is warranted [1,4].

In the vast majority of encountered pancreatic cysts, the lesion is small (less than 2.5 cm) and worrisome features are absent. In this scenario, clinical and imaging follow-up are reasonable courses of action. However, debate exists

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Table 1. Summary of high-risk features of cystic lesions based on current guidelines

High-risk feature	ICG	AGA	ACG	EG	ACR
Presence of enhancing mural nodule/solid component	+	+	+	+	+
Dilation of the main pancreatic duct > 5 mm	+	+	+	+	+ (7 mm)
Abrupt change in caliber of the pancreatic duct	+		+		
Size of cyst larger than 3–4 cm	+ (3 cm)	+ (3 cm)	+ (3 cm)	+ (4 cm)	+ (3 cm)
Interval growth*	+ (2.5 mm/year)	+	+ (3 mm/year)	+ (5 mm/year)	+
Positive cytology on fluid aspiration	+		+	+	

*Specific rate of interval growth is defined for some guidelines, listed above, with the exception of ACR, which defines specific growth rates based on size of the lesion at initial presentation, ranging from 20% increase to 100% increase in longest dimension.
ICG = International Consensus Guideline, AGA = American Gastroenterological Association, ACG = American College of Gastroenterology, EG = European Guidelines, ACR = American College of Radiology, + = mention of high-risk feature in that guideline, and blank cells indicates absence of mention of that feature

regarding whether follow-up should be performed with CT or MRI. The ACR white paper specifies that either imaging modality is acceptable, given the absence of a documented significant difference in performance between the two modalities. However, the ACG and AGA guidelines specify MRI with MRCP due to its ability to differentiate side branch communication and avoid radiation exposure [1,14,15]. Additionally, MRI is preferred due to the increased sensitivity of the modality for identifying septations and mural nodules. However, CT may be preferred by gastroenterologists and surgeons and is highly sensitive in detecting calcifications within the lesion. A debate exists regarding the frequency and duration of follow-up imaging. Some guidelines recommend 5 years of stability; others, including the ACR, suggest up to 10 years of follow-up [1,11,14-16], with initial imaging every 6 months for certain lesions. We believe that lengthening the interval between follow-up scans is reasonable provided that the lesion is small (less than 1 cm). Furthermore, 10 years of follow-up may be excessive as the risk of malignant transformation in these lesions after 5 years is low [17].

Multiple guidelines suggest an aggressive approach for large lesions (2.5 to 4.0 cm) at presentation, even in the absence of worrisome features. Interval growth is also associated with possible progression, and an aggressive approach is warranted [1,12,14,16].

If worrisome features are present regardless of tumor size, an aggressive approach should be undertaken, including EUS with aspiration and consideration of surgery. These features include mural nodules (Fig. 5), main pancreatic duct dilatation with or without abrupt caliber change (Fig. 6), solid components, or peripheral calcifications (Fig. 7) [1,12,14,16].

If a lesion has the characteristic appearance of a serous cystadenoma, diagnosis based on imaging alone is reasonable, thus obviating the need for additional follow-up in line with the ACR, AGA, and ACG guidelines.

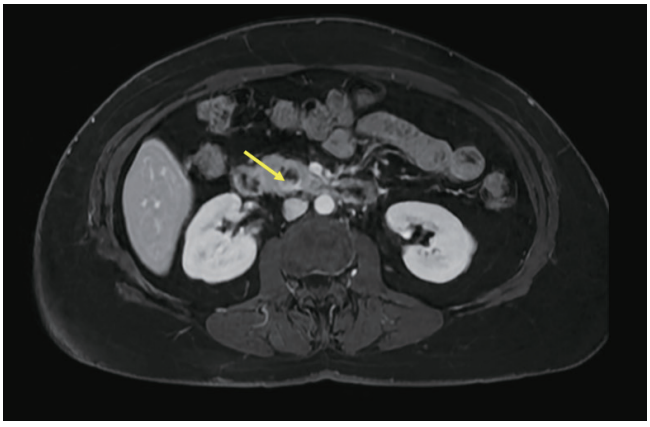

Fig. 5. Axial T1 weighted, fat-saturated, contrast-enhanced portal venous phase MRI of a 57-year-old female displays enhancing mural nodularity measuring 5 mm (arrow) in a pancreatic cystic lesion measuring 1.7 cm in the uncinate process, a concerning feature. Endoscopic ultrasound with fine-needle aspiration is recommended based on these findings. Pathology revealed well well-differentiated neuroendocrine tumor, undergoing surveillance.

These are new insights into the pathophysiology of IPMNs. Some IPMNs are macroscopic precursors of ductal adenocarcinoma, which may occur in a different location within the gland. Progression to ductal adenocarcinoma is associated with KRAS and GNAS mutations [7,18,19]. Such mutations can be detected using cyst fluid analysis. The development of molecular markers is anticipated to enhance patient management and further refine the monitoring of patients who should be closely observed for the development of carcinoma elsewhere in the gland. We hope for, and expect an update to the imaging follow-up guidelines for these patients.

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CONCLUSION

In summary, our approach to the incidental pancreatic cyst is to carefully evaluate the lesion for increased size and worrisome features. If the lesion is greater than 2.5 cm or exhibits any worrisome features, we suggest referral to a pancreatic center in anticipation of EUS and fine-needle aspiration. If a lesion is less than 2.5 cm and free of worrisome features, we recommend follow-up imaging. Our opinion is in line with the major guidelines on suspicious features. Our size-based recommendations centered around 2.5 cm are in line with the most up-to-date guidelines from the ACR and are slightly more conservative compared to the EG, AGA, and ACG recommendations based on 3–4 cm. This approach allows for improved sensitivity. If a patient has comorbidities that preclude resection or declines resection if offered, then no follow-up imaging is appropriate, in concordance with the guidelines.

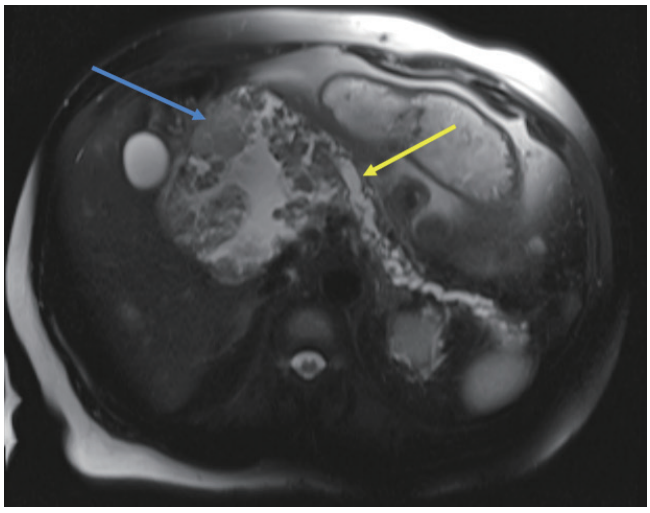

Fig. 6. Axial, T2 weighted MRI of a 60-year-old male demonstrates diffuse pancreatic ductal dilation measuring up to 9 mm (yellow arrow) to the level of a large pancreatic cystic lesion in the pancreatic head measuring up to 11.8 cm with solid components measuring up to 4.2 cm (blue arrow). Both of these are considered concerning features. The patient underwent a Whipple procedure based on these findings, and pathology revealed intraductal oncocytic papillary neoplasm without invasive carcinoma.

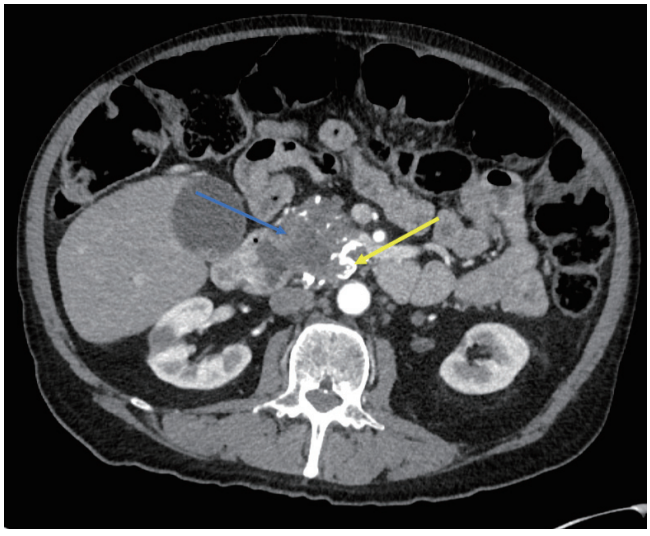

Fig. 7. Axial, contrast-enhanced portal venous phase CT image of a 71-year-old male. A cystic lesion is observed in the pancreatic head measuring 4.2 cm with peripheral calcifications (yellow arrow) and solid components measuring up to 1.7 cm (blue arrow), two concerning features. Based on these findings he underwent endoscopic ultrasound with fine-needle aspiration, with pathology revealing mucinous cystic neoplasm with invasive carcinoma.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Writing—original draft: Erik K. Paulson. Writing—review and editing: Danielle E. Kruse.

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