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Calcified pancreatic and peripancreatic neoplasms: spectrum of pathologies

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Abstract

A variety of pancreatic and peripancreatic neoplasms may contain calcifications. We present a review of common to uncommon pancreatic neoplasms that may contain calcifications to include ductal adenocarcinoma, pancreatic neuroendocrine tumors, serous cystadenomas, solid pseudopapillary tumors, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and lymphoepithelial cysts. In addition, duodenal mucinous adenocarcinoma can present as a peripancreatic mass that may contain calcification. Knowledge of the spectrum of calcification patterns can help the interpreting radiologist provide a meaningful differential.

Key words: Pancreas—Calcification—Computed tomography

A variety of pancreatic and peripancreatic neoplasms may contain calcifications. Knowledge of what lesions may calcify and the patterns of calcifications can help the interpreting radiologist hone in on a specific diagnosis or refine a differential diagnosis which may alter management.

Common pancreatic neoplasms that may contain calcifications

Ductal adenocarcinoma

Pancreatic ductal adenocarcinoma represents the twelfth most common cancer with an incidence of 48,960 new cases in the United States and 40,560 deaths in 2015 according to the surveillance, epidemiology, and end results (SEER) Program. This accounts for 3% of all new cancer cases and 6.9% of cancer deaths. It has an abysmal 5-year survival of a mean 7.2% for all stages, 27% for localized disease, and 2.4% for metastatic disease. It is slightly more common in men with a mean age of diagnosis of 70 years. It accounts for 85% of all pancreatic neoplasms. They can be found incidentally or during workup for jaundice [1].

Up to 70% of tumors are localized to the pancreatic head, 25% to the body and tail. On CT imaging, tumors appear as a solid, hypovascular mass that frequently causes ductal obstruction. They are best seen in venous phase imaging but occasionally may become isodense during venous phase. Calcification, while uncommon, can be punctate or coarse (Fig. 1). The etiology of calcification has not been confirmed but postulated to be dystrophic, related to necrosis, in the absence of chronic pancreatitis change. The presence of calcification should not dissuade the radiologist from raising concern for adenocarcinoma, particularly in the setting of an obstructing pancreatic head mass [2]. Patients with chronic calcifying pancreatitis are at higher risk for adenocarcinoma and may develop tumor around calcifications, which can appear punctate to large clusters. In a 2017 series of 48 patients, Mohamed et al. demonstrated scarce calcifications in 22%, abundant calcifications in 44%, and very abundant calcifications in 33% of their patients with chronic calcifying pancreatitis that developed cancer as an obvious hypodense mass that displaced pancreatitis calcifications [3].

Uncommon pancreatic neoplasms that may contain calcifications

Pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors (PNETs) account for 1–2% of all pancreatic tumors with an annual incidence of less than 1 per 100,000, typically seen in older adults [4–6]. Small lesions are frequently found incidentally when imaging for other reasons or present with a related hormonal syndrome. Nearly all well-differentiated PNETs have been found to produce some hormones.

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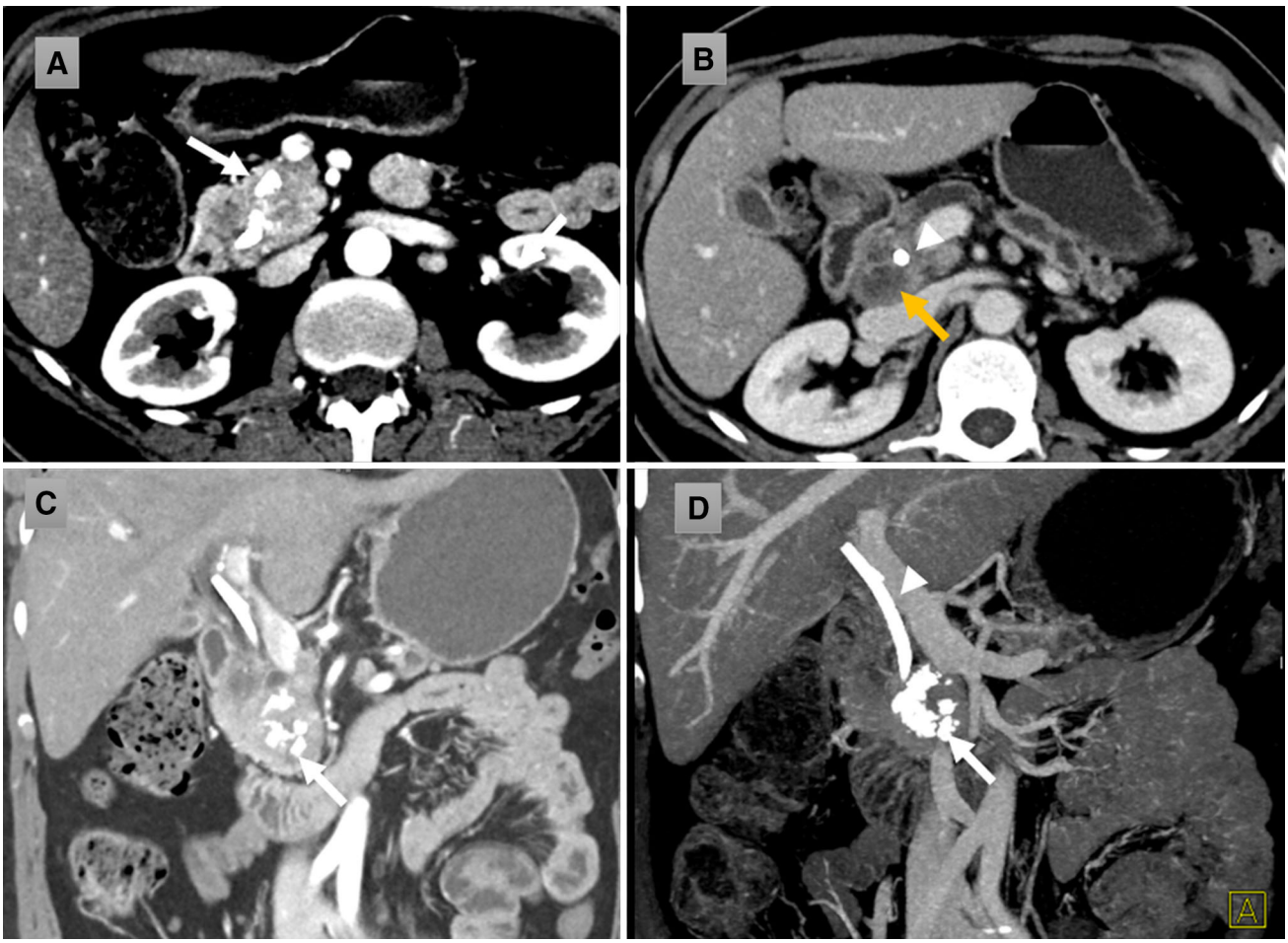

Fig. 1. 49-year-old woman with pancreatic mass. IV contrast-enhanced CT with axial arterial phase (**A**), axial venous phase (**B**), coronal arterial phase (**C**), and coronal thick-slab MIP venous phase (**D**) images. Obstructing pancreatic head/uncinate process mass seen with ill-defined hypoattenuation and extensive coarse calcification (*white arrows*). A typical discrete hypodense mass is not seen. Peripancreatic necrotic adenopathy is present (*gold arrow*). A common bile duct stent is in place (*arrow head*). ERCP brushing revealed adenocarcinoma of pancreatic primary. There is no reported history of pancreatitis although calcifications were present throughout the pancreas to suggest prior pancreatitis (not shown).

Most patients do not present with an endocrinopathy as the hormones are produced in small quantities and are considered non-hyperfunctioning or non-functional. When symptoms of a paraneoplastic endocrinopathy are present, the tumors are considered hyperfunctioning or functional [6, 7].

On imaging, tumors can range from small vascular masses to large heterogeneous cystic masses. They usually do not obstruct the duct as with adenocarcinoma. Larger tumors can have vascular invasion, especially into the portal, superior mesenteric, or splenic veins, unlike adenocarcinoma which typically narrows and encases vessels. Increasing tumor size has been associated with cystic necrosis and subsequent development of dystrophic calcifications [8]. Calcifications more commonly occur within non-functioning and larger neoplasms. Insulinoma represents the most common functional PNET. They are usually small at diagnosis, which may

Table 1. Summary of calcifications in pancreatic and peripancreatic masses

Tumor	Frequency of calcification	Usual pattern of calcification	Usual location of calcification	Extent of calcification	Comments
Ductal adenocarcinoma	Rare	Punctate or coarse	Random	Focal	Intratumoral versus related to pancreatitis
Pancreatic neuroendocrine tumor	Uncommon	Coarse	Central	Focal	More common in larger tumors
Serous cystadenoma	Uncommon	Stellate	Central	Focal	Calcifications in oligocystic variants can mimic mucinous tumors
Solid pseudopapillary tumor	Common	Coarse	Peripheral	Focal to extensive	Increasing calcification with hemorrhage
Intraductal papillary mucinous neoplasm	Uncommon	Punctate	Peripheral	Focal	Coarse calcification associated with malignancy
Mucinous cystic neoplasm	Uncommon	Eggshell or punctate	Peripheral	Focal to diffuse	Malignant feature
Lymphoepithelial Cyst	Rare	Punctate	Peripheral	Focal	No concern
Duodenal mucinous adenocarcinoma	Uncommon	Punctate or coarse	Random	Focal to diffuse	Malignant feature

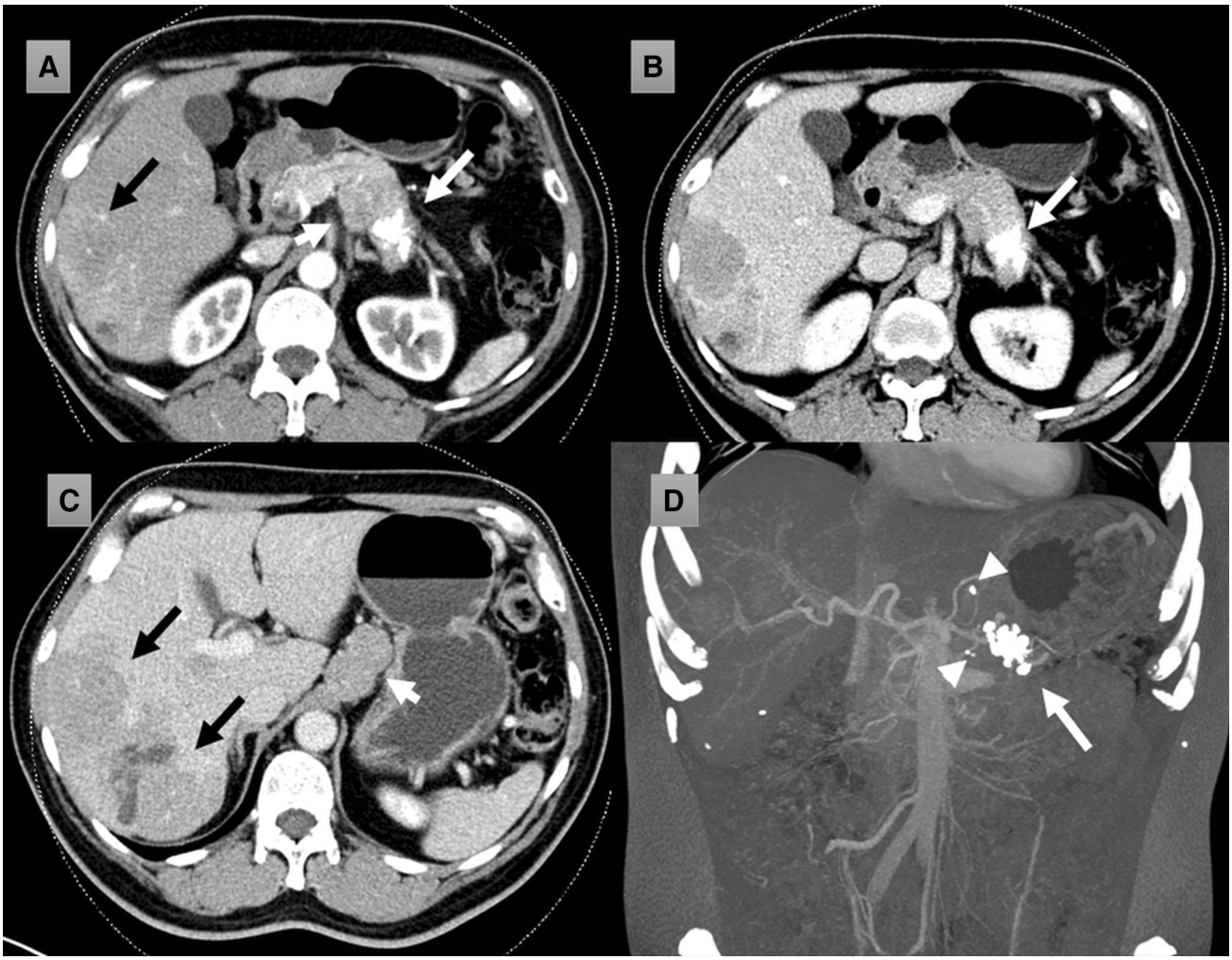

Fig. 2. 58-year-old man with pancreatic mass. IV contrast-enhanced CT in axial arterial (**A**) and portal venous phases (**B**, **C**) demonstrate a cluster of coarse calcifications in the pancreatic tail (*white arrows*) with adenopathy (*short white arrows*) and hepatic metastatic disease (*black arrows*). Coronal thick-slab MIP (**D**) depict the calcifications throughout the mass and punctate calcifications in the metastatic gastrohepatic and peripancreatic adenopathy (*arrow heads*). Liver biopsy revealed a well-differentiated neuroendocrine tumor. Patient was not a surgical candidate and received chemotherapy.

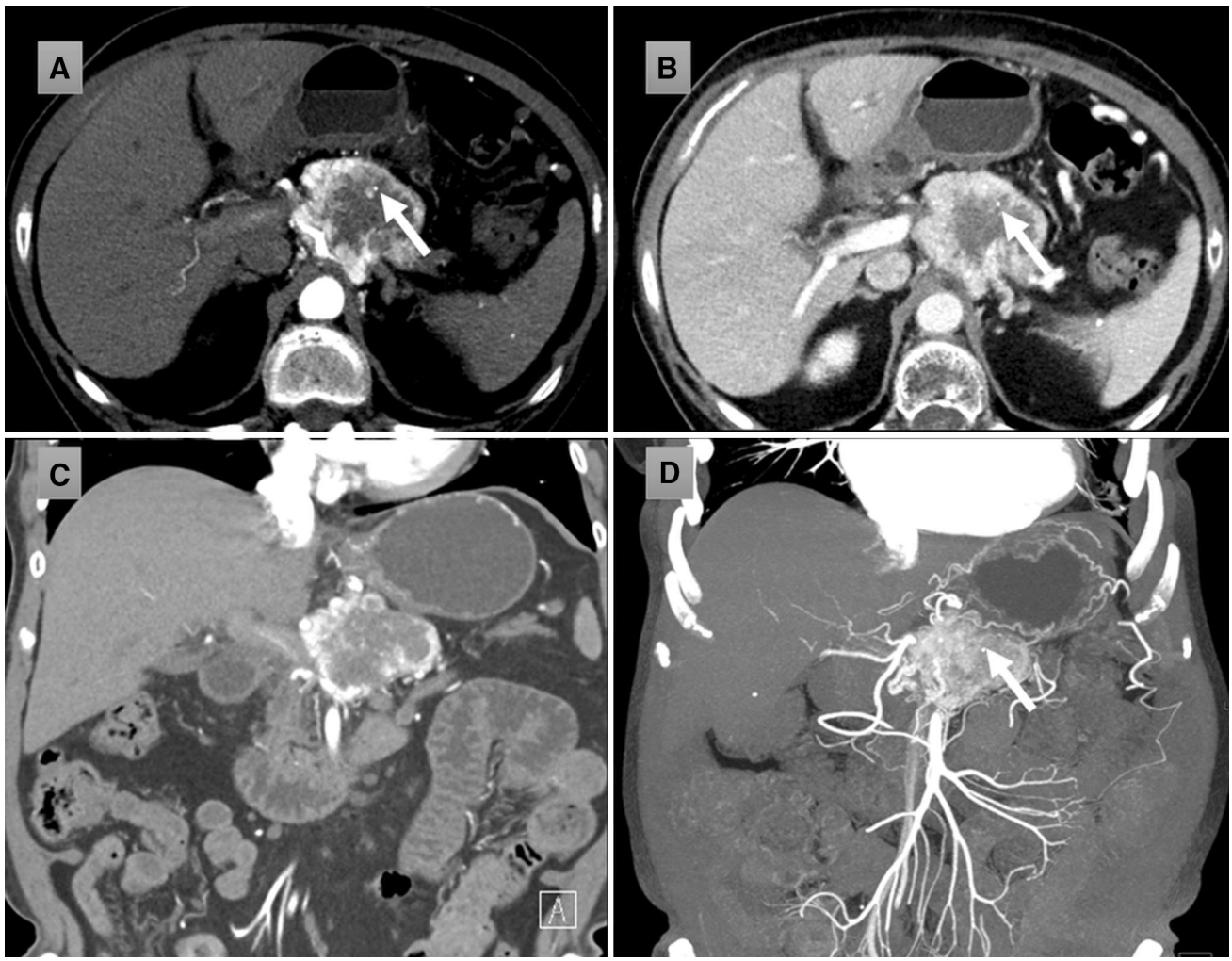

Fig. 3. 67-year-old woman with pancreatic mass. IV contrast-enhanced CT in axial and coronal arterial (**A**, **C**) and portal venous phases (**B**) demonstrate a 6-cm heterogenous peripherally enhancing mass with a punctate calcification (*arrow*). Coronal thick-slab MIP reconstruction (**D**) demonstrates the vascularity of the mass with punctate calcification (*arrow*). FNA demonstrated a well-differentiated neuroendocrine tumor. Patient was not a surgical candidate and received chemoradiation.

contain calcifications in up to 20% of cases. Calcifications can be found in PNETs in up to 16% of cases. Calcifications are usually focal, coarse, irregular, and centrally located [8, 9] (Figs. 2, 3).

Serous cystadenoma

Serous cystadenomas are benign cystic tumors frequently found in woman in the 5th to 7th decades. They are usually located in the pancreatic head. Small tumors are usually incidentally found. Tumors great than 4 cm are more likely to be symptomatic. Three morphologic types are seen at imaging which include polycystic (70%), honeycomb (20%), or oligocystic (10%). The polycystic variant contains cystic components less than 2 cm. Lobulations and a central scar are seen with this variant. Stellate central calcification is seen in a third of cases (Fig. 4). The etiology of formation of calcification remains unknown. Oligocystic variants contain cystic components greater than 2 cm. Oligocystic variants can

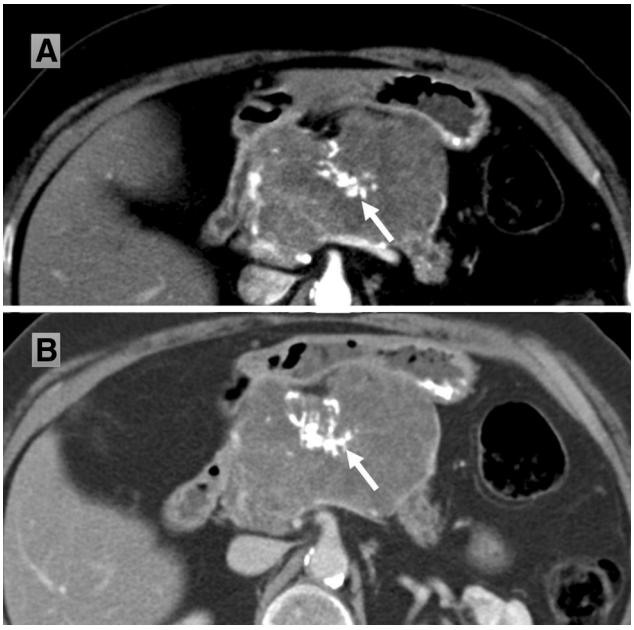

Fig. 4. 71-year-old woman with symptomatic pancreatic mass. IV contrast-enhanced CT in axial arterial (**A**) and portal venous phases (**B**) demonstrate an 8.6 × 6 cm hypovascular mass with microcystic appearance and prominent rim vascularity. Central cluster of coarse calcifications is present (*arrows*). Patient was a surgical candidate and underwent Whipple procedure demonstrating a serous cystadenoma.

mimic mucinous tumors however usually do not contain mural calcification as mucinous tumors can demonstrate. Honeycomb variant contain tiny cysts which at times can appear as a solid mass [10–12].

Solid pseudopapillary tumor

Solid pseudopapillary tumors (SPTs), also known as solid pseudopapillary epithelial neoplasms (SPENs), are rare pancreatic tumors, accounting for only 1%–2% of pancreatic exocrine neoplasms, occurring predominately in women in the second or third decade [13–15]. SPTs are typically large at diagnosis, with a report mean diameter of 9 cm. Recent studies have categorized SPTs into small (≤3 cm) and large tumors (≥3 cm) with separate imaging findings. Large SPTs are typically well demarcated, encapsulated appearing masses with peripheral solid and central cystic components. Calcifications, usually peripheral, are seen in 65% of cases (Fig. 5) [16]. Contradistinction to large SPTs, small SPTs are homogeneous, solid masses with less frequent calcification, which can mimic adenocarcinoma or PNET. Atypical SPTs may demonstrate massive dense calcification or rarely curvilinear or stippled calcification [5]. Calcifications are thought to be dystrophic following intratumoral hemorrhage or cystic change, typical of SPT [17].

Intraductal papillary mucinous neoplasm

Intraductal papillary mucinous neoplasms (IPMNs) account for up to 7% of all pancreatic neoplasms, typically in older male patients (5:1 male to female), 60 to 70 years old. They are categorized by location as branch duct, main duct, or mixed types. There are four histologic subtypes which include gastric, intestinal, pancreaticobiliary, and oncocytic where gastric and intestinal subtypes comprise the majority of subtypes [18–20].

IPMNs occur usually in the head and uncinate process in up to 70% of cases. On imaging, branch-duct IPMNs can appear unilocular or multilocular cystic masses, whereas main-duct types appear as main duct dilation, currently set at 5 mm or greater by international consensus guidelines. All IPMNs have some malignant potential. Malignant features or features predictive of malignancy include large size greater than 3 cm, mural nodularity and duct obstruction [21, 22].

Calcifications, typically mural, have been reported in up to 25% of IPMNs with punctate calcification seen in approximately 90% of cases. Coarse and eggshell calcifications have also been described. The presence of punctate calcification (Fig. 6) has not been associated with malignancy. However, coarse calcifications when present are highly associated with malignancy (Fig. 7). Although the exact mechanism for calcification is unknown, it is thought that thick mucin binds calcium salts [23–25].

Mucinous cystic neoplasm

Pancreatic mucinous cystic neoplasms (MCN) are rare tumors nearly exclusively found in women (20:1 women to men) who are 40–60 years old. Patients are usually

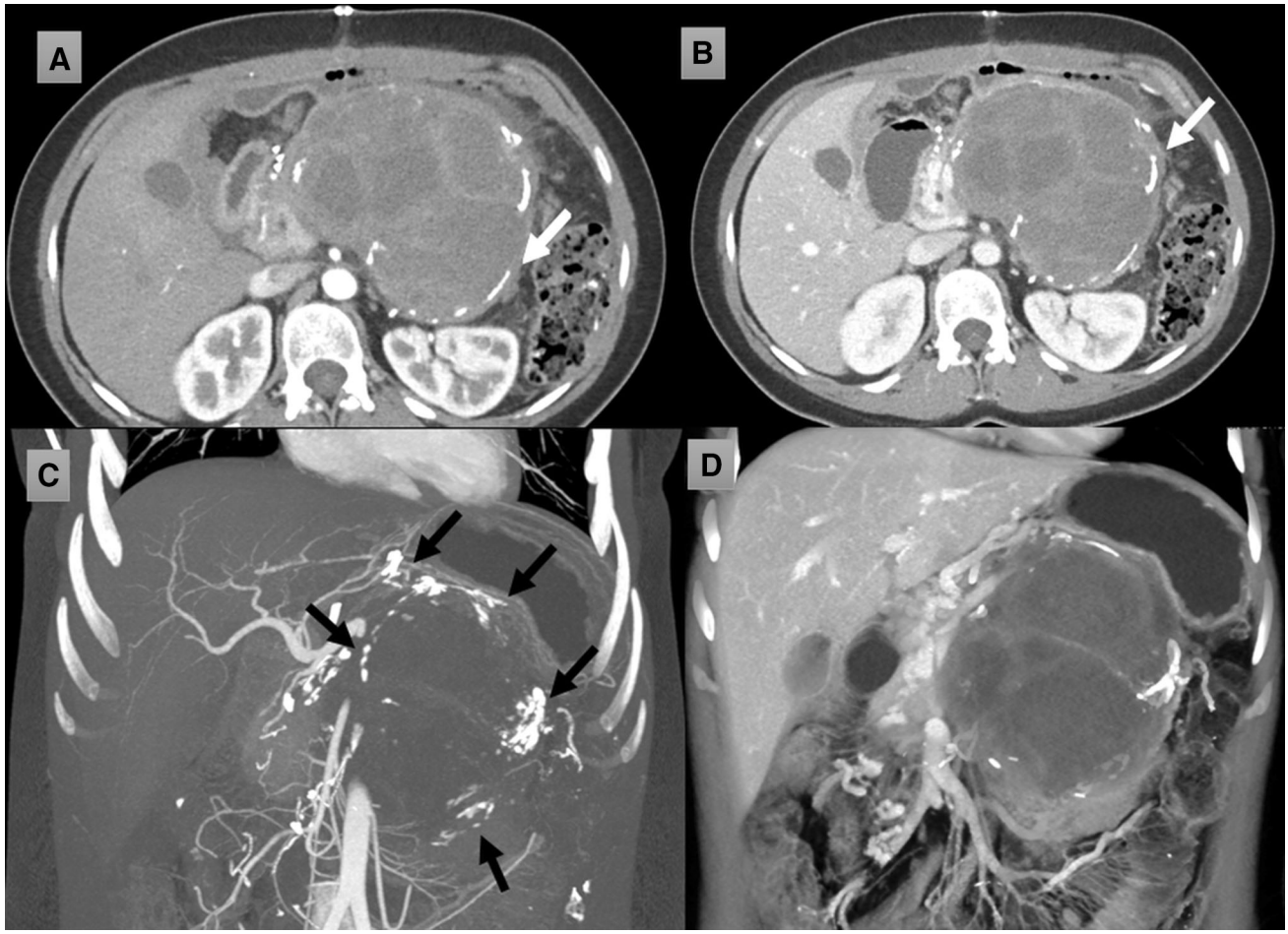

Fig. 5. 30-year-old woman with pancreatic mass. IV contrast-enhanced CT in axial arterial (**A**) and venous (**B**) phases with coronal thick-slab MIP (**C**) and 3D rendering (**D**) demonstrate a large pancreatic mass with rim interrupted calcifications (*arrows*). Mass demonstrates soft tissue and cystic components. MIP imaging fully depicts all the calcification in one image (*black arrows*). Mass was resected and revealed a solid pseudopapillary tumor (SPT).

asymptomatic or complain of vague abdominal or back pain, nausea, vomiting, or present with pancreatitis [26].

They are differentiated from other pancreatic mucin producing neoplasms such as intraductal papillary mucinous neoplasms with the presence of ovarian-type stroma. Estrogen and progesterone receptors have been demonstrated in this ovarian-type stroma which may explain the predominance in women [27].

On imaging, MCNs are nearly always found in the body or tail without ductal communication. Size can range from small to very large (2–36 cm). Septations may be seen which can create a multilocular appearance. MCNs do have malignant potential which should be suggested when the MCN is larger than 2 cm or when irregularity or nodularity of the wall and/or septation is discovered. MCNs can calcify with peripheral eggshell or focal punctate calcifications (Fig. 8) in up to 25% of cases. The mechanism of calcification is uncertain, probably dystrophic. This should also be reported as potential malignant feature [28–30].

Lymphoepithelial cyst

Lymphoepithelial cysts (LECs) are very rare, non-malignant, true pancreatic cysts, seen in less than 1% of pancreatic cystic neoplasms. Cysts are lined with squamous epithelium and surrounded by mature lymphoid tissue. They are frequently seen in middle age men (4–7:1 men to women) contrary to other pancreatic cystic masses which are typically seen in women [18, 31].

On imaging, LECs are appeared as exophytic masses arising near the surface of the pancreas. There is no site

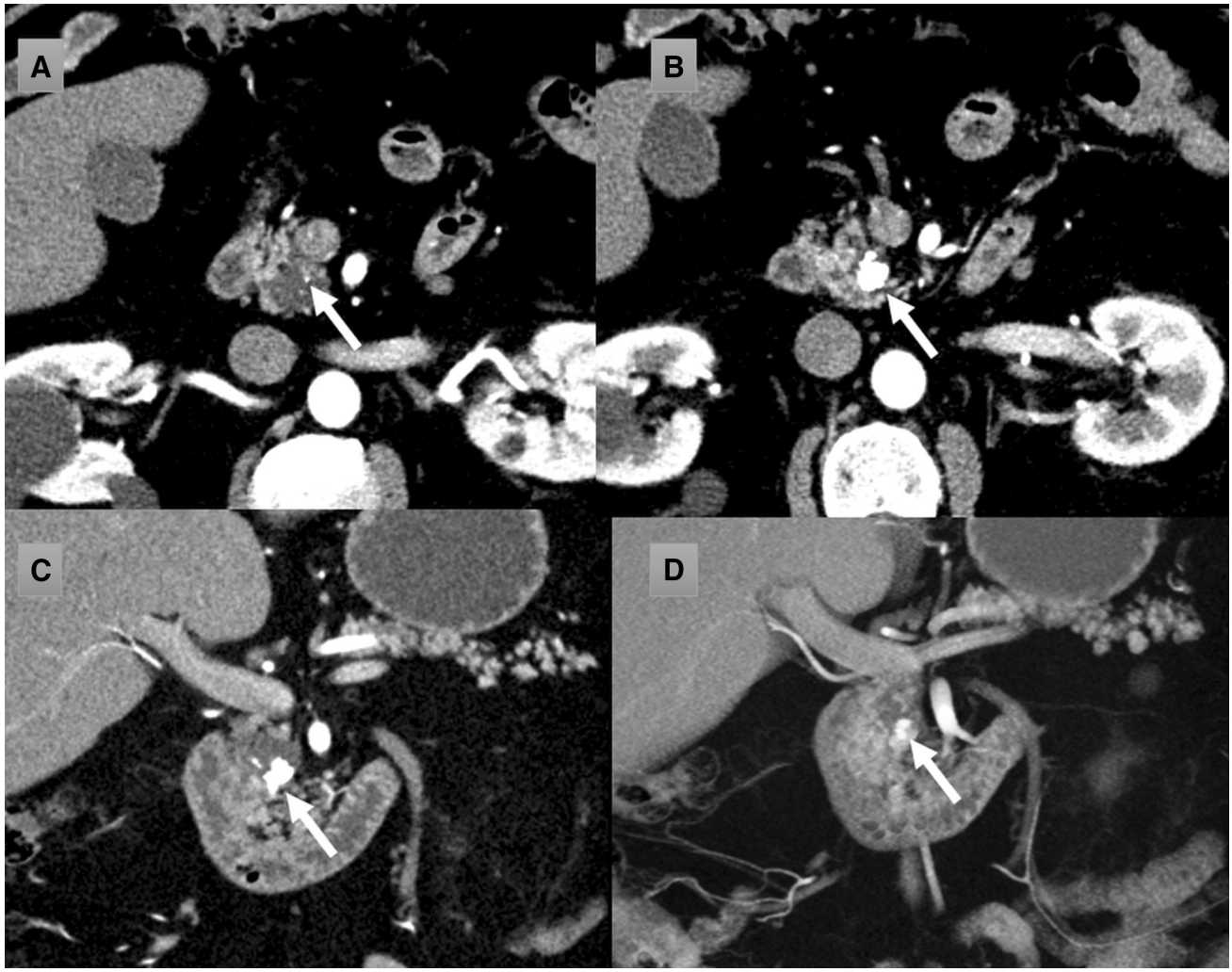

Fig. 6. 68-year-old man with pancreatic mass. IV contrast-enhanced CT in axial arterial phase (**A**) and axial, coronal, and coronal 3D portal venous phase (**B**, **C**, **D**) demonstrates 1.5 × 2 cm pancreatic head cystic mass with eccentric cluster of coarse calcifications (*arrow*). Additional punctate calcification seen cranial to larger cluster (**A**, *arrow*). EUS/FNA was performed demonstrating mucinous features and communication with pancreatic duct, consistent with an intraductal papillary mucinous neoplasm.

predilection. Sizes can range from subcentimeter to nearly to 20 cm with an average of 4.5 cm. The internal contents can be complex appearing due to the granular keratinized material within the cyst fluid. Enhancing septations are common in up to 50% of cases yielding a multilocular appearance. LECs rarely calcify but are usually peripheral punctate to coarse when found (Fig. 9). Origin of calcifications is uncertain but may be related to keratinous plugs, squamous metaplasia, or granulomas in the lymphoid tissue [32, 33].

Peripancreatic neoplasms that may contain calcifications

Duodenal adenocarcinoma

Small bowel cancers are rare tumors, comprising less than 5 percent of all gastrointestinal cancers with up to 23 cases per million persons in 2004 reported by SEER [34, 35]. Adenocarcinoma accounts for up to 40% of all small bowel cancers. Patients are usually in their sixth decade of life without sex predilection. The duodenum is

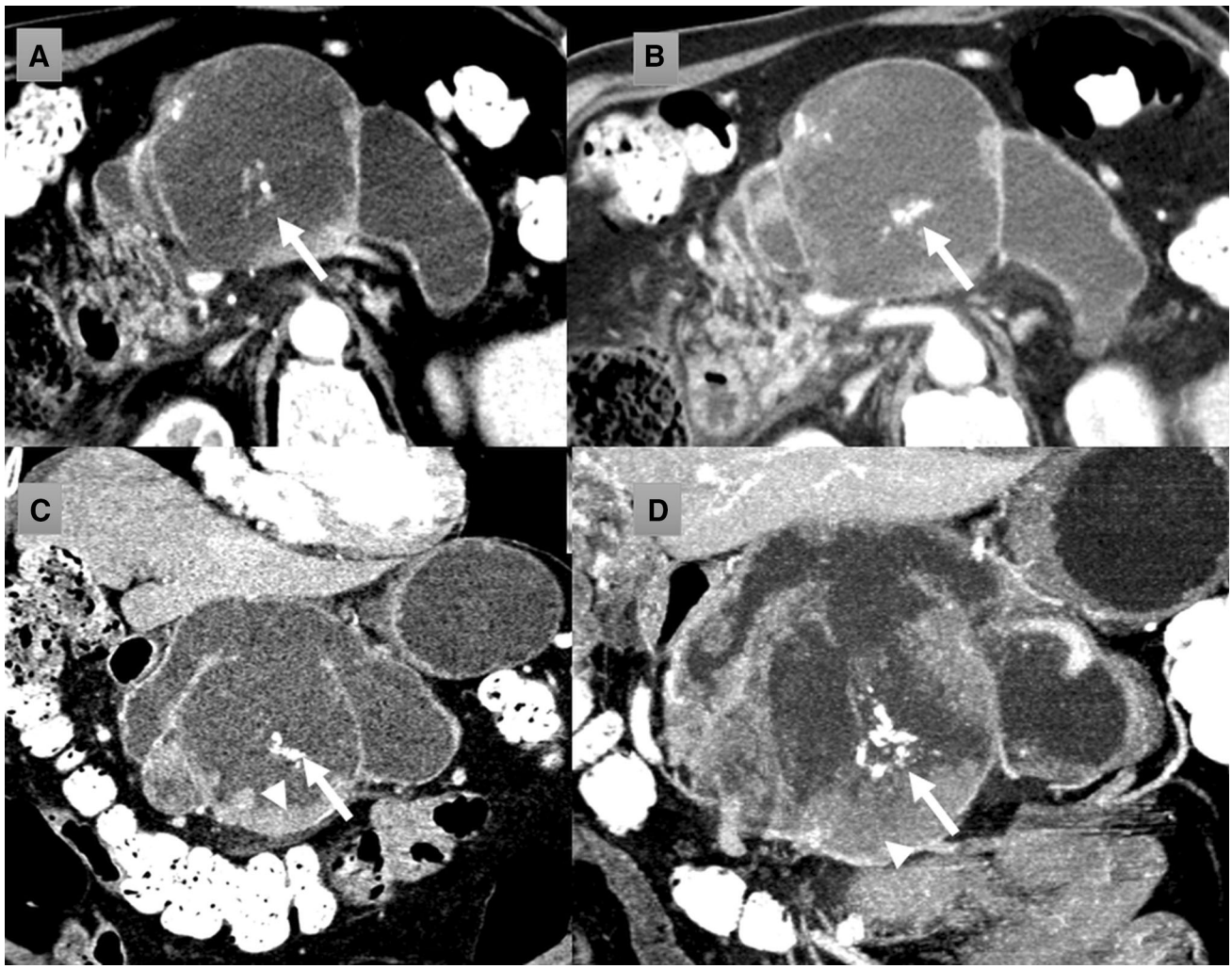

Fig. 7. 69-year-old man with pancreatic mass. IV contrast-enhanced CT in axial arterial phase (**A**) and in axial, coronal, and MIP portal venous phase (**B**, **C**, **D**) demonstrates massive dilation and sacculation of the main duct with extensive mural nodularity (*arrows heads*) and areas of coarse calcification (*arrows*). Partially imaged pancreatic head is enlarged with acute pancreatitis (not labeled). Patient underwent distal pancreatectomy revealing colloid carcinoma arising from IPMN. Nodal and omental metastases were present (not shown).

the most common tumor site in up to 50% of cases followed by jejunum then ileum. The periampullary region is the most common location. The adenoma-carcinoma sequence, similar to colon cancer formation, has been observed for duodenal carcinomas. Additional risk for carcinoma increases in the presence of genetic syndromes such as familial adenomatous polyposis and Peutz-Jeghers syndrome. Celiac and Crohn's diseases are additional risk factors with tumor forming more commonly in the jejunum and ileum, respectively. Patients are usually symptomatic with pain, weight loss, obstructive symptoms, bleeding, and rarely perforation. Mucinous

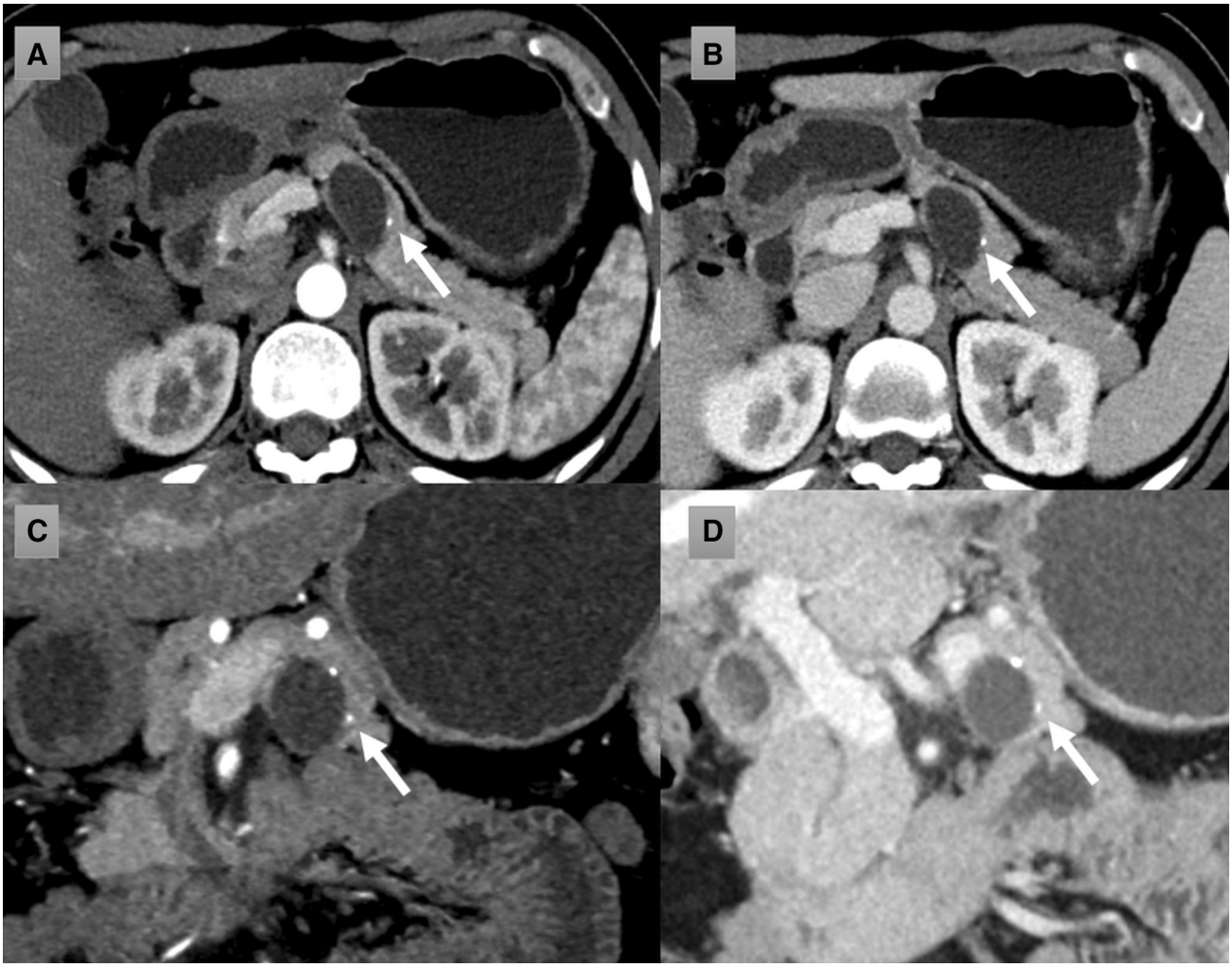

Fig. 8. 48-year-old woman with pancreatic mass. IV contrast-enhanced CT in axial arterial phase (**A**) axial venous (**B**), coronal arterial (**C**), and coronal venous (**D**) phases. Well demarcated, 3 cm, partially exophytic, cystic mass, arising from the pancreatic body. No internal septation or debris was present. Two punctate calcifications are seen (*arrows*). No communication with duct was noted. Patient underwent EUS-FNA revealing very high CEA levels, consistent with a mucinous cystic neoplasm.

subtypes exist, similar to other bowel mucinous adenocarcinoma subtypes, may contain uncommon variable punctate to coarse calcification, likely dystrophic (Fig. 10) [36, 37].

Conclusion

This review article describes the common to uncommon pancreatic and peripancreatic neoplasms that may contain calcifications (Table 1). Some neoplasms contain calcifications more frequently than others. The inter-

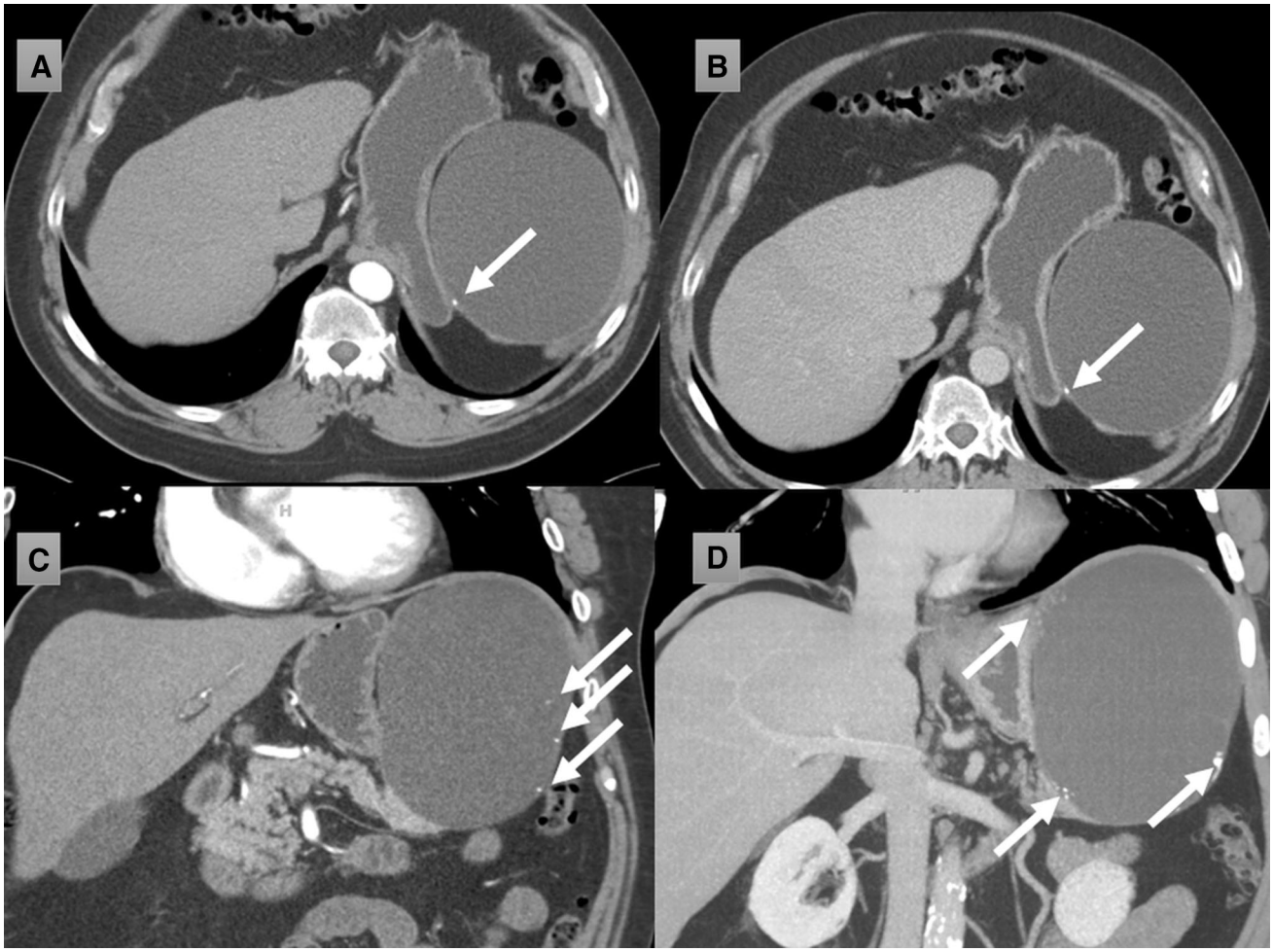

Fig. 9. 66-year-old man with peripancreatic mass. IV contrast-enhanced CT with selected axial arterial (**A**), axial venous (**B**), coronal arterial (**C**), and coronal thick-slab MIP arterial (**D**) images. Large round exophytic cystic mass arising near the tail of the pancreas, measuring 14 × 12 × 15 with mass displacement of the stomach. Note punctate and coarse calcifications along the wall (*arrows*). Patient had a prior distal pancreatomy and splenectomy for resection of similar mass. Resection demonstrated recurrent lymphoepithelial cyst without evidence of carcinoma.

preting radiologist should not be dissuaded from an important diagnosis of adenocarcinoma if calcification is found. Knowledge of the frequency and pattern of calcification in the other uncommon neoplasms can help the radiologist hone into a specific diagnosis or refine the differential diagnosis.

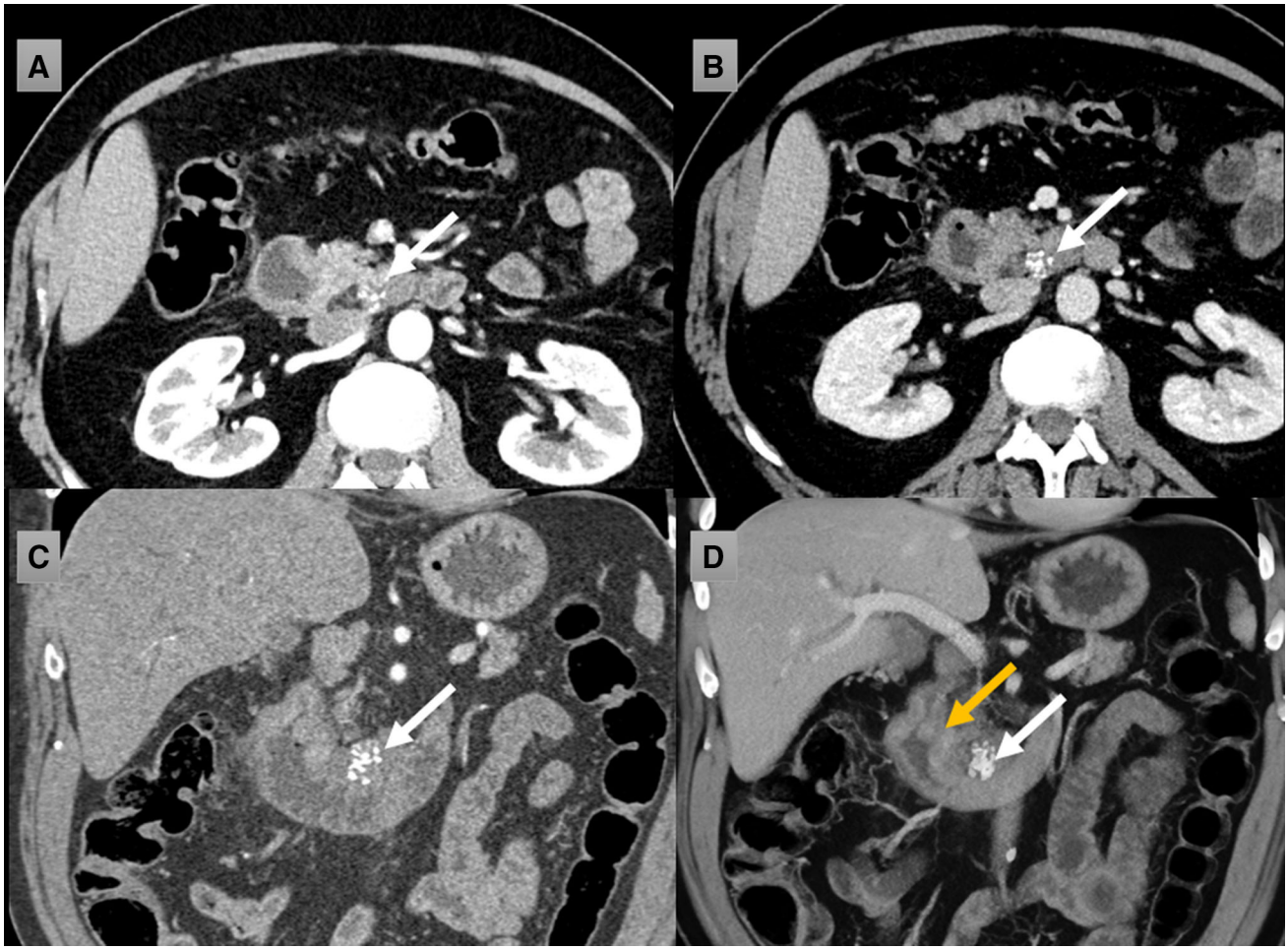

Fig. 10. 65-year-old man with peripancreatic mass. IV contrast-enhanced CT with selected axial arterial (**A**) and portal venous phases axial (**B**), coronal (**C**), and coronal 3D (**D**) images. Cluster of calcifications noted near the uncinate process abutting third portion duodenum (*white arrows*). Subtle thickening of the 2nd portion duodenum near the ampulla also seen, best depicted on 3D image (*gold arrow*). Histology revealed a 4.1-cm mucinous adenocarcinoma with pancreatic invasion and regional metastatic adenopathy (not shown).

Compliance with ethical standards

Funding No funding was obtained for this study.

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent waiver was obtained by institutional review board for this the study.

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