Pancreatic Neoplasms: CT Evaluation of the Uncommon Presentations of Common Lesions and Common Presentations of the Uncommon Lesions!

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Abstract
Pancreatic masses are commonly encountered entities in radiology practice. Pancreatic ductal adenocarcinomas (PDAC) are the commonest pancreatic malignancies that typically present as infiltrative hypodense focal masses in the pancreatic head, which are hypoattenuating to the pancreatic parenchyma on pancreatic parenchymal and venous phases. However, there are various atypical imaging features of PDACs that create a diagnostic dilemma like tumor in body or tail, diffuse glandular involvement, isoattenuating tumors, cystic changes, or calcifications. Also, few relatively uncommon pancreatic malignancies like pancreatic neuroendocrine tumors, cystic pancreatic tumors, pancreatic lymphoma, and pancreatic metastases present with overlapping features. Accurate radiological characterization of pancreatic masses is important for optimal management and prognostication. Thus, it is imperative for radiologists to be aware of all the uncommon presentations of common pancreatic lesions and common presentations of uncommon pancreatic lesions to avoid erroneous interpretations and establishing the correct diagnosis.

Keywords
► pancreatic ductal adenocarcinoma
► neuroendocrine tumors
► cystic pancreatic tumors
► pancreatic lymphoma
► pancreatic metastases

Introduction
Pancreatic neoplasms are commonly encountered entities in clinical practice. Pancreatic ductal adenocarcinomas (PDACs) are the most common of all pancreatic malignancies, which show few typical imaging features aiding in radiological diagnosis. However, PDACs may show few atypical features that lead to a diagnostic dilemma. Also, many other pancreatic neoplasms may present with overlapping imaging characteristics, which further complicate the diagnosis. It is imperative for radiologists to be aware of all the uncommon presentations of common pancreatic neoplasms and common presentations of uncommon pancreatic neoplasms to avoid erroneous interpretations and establish the correct diagnosis.

Pancreatic Ductal Adenocarcinoma
PDACs account for approximately 90% of all pancreatic malignancies with the most common site of origin being head of pancreas (approximately 60–70%), and remainder found in body (approximately 15%) and tail (15%).1 Tumors in the body (►Fig. 1) and tail (►Fig. 2) tend to assume a large size before producing clinical symptoms, due to the lack of obstructive symptoms of the biliary and gastric systems and hence they tend to have a poorer prognosis.
Majority of the PDACs present as infiltrative hypodense masses on computed tomography (CT), which are hypoattenuating to the pancreatic parenchyma on pancreatic parenchymal and venous phases. On magnetic resonance imaging (MRI), PDACs are hypointense on T1-weighted imaging (T1WI) and hyperintense on T2WI, and show restricted diffusion on diffusion-weighted imaging (DWI) and are hypoenhancing to the normal pancreas on arterial and venous phase.

A few PDACs may be isoattenuating to pancreas, with no visible pancreatic mass in up to 10% of cases, which are detected due to secondary signs such as mass effect, contour bulge, pancreatic duct (PD) obstruction, and upstream dilatation. Sheathing of the celiac trunk and/or superior mesenteric artery is seen in 30 to 60% of CT scans of PDAC, which may be a sign of an isodense tumor. This is also described in cases of autoimmune pancreatitis (AIP) or extrapancreatic lesions in sclerosing mesenteritis and retroperitoneal fibrosis and hence is not considered as pathognomonic. DWI may be used in these tumors that are isoattenuating on CT and dynamic contrast-enhanced (DCE) MRIs.

PDACs usually manifest as an area of increased uptake within the pancreas on fluorodeoxyglucose-positron emission tomography (FDG-PET), thus being useful in depicting small pancreatic lesions (<2 cm) that are difficult to detect on CT or isoattenuating lesions, and also for lesion characterization. Based on tumor biology and the degree of desmoplastic response, PDACs may sometimes demonstrate a low level or no FDG uptake.

PDACs may present as diffuse glandular infiltration in up to 5% of cases or with cystic changes in up to 8% of cases. Cyst-like features found in PDACs in a study done by Kosmahl et al represented cystic degeneration or tumor necrosis, retention cysts or side-branch ductal obstruction, and adjacent pseudocysts. PDACs do not commonly show calcifications. Calcifications in PDACs may be explained by the pre-existing chronic calcific pancreatitis or secondary to PD obstruction. In a study done by Campisi et al, 3.9% of pancreatic calcifications were seen in patients with PDACs, with three of the four patients showing calcifications within the nonneoplastic pancreatic tissue and calcification within the adenocarcinoma was seen in only one patient without underlying chronic calcific pancreatitis.

**Mimics of PDACs**

Various inflammatory diseases may radiologically mimic PDAC. Chronic mass forming pancreatitis (CM-FP) may show similar morphological and enhancement characteristic as PDACs. However, CM-FP usually shows “duct penetrating sign,” in which a nonobstructed or smoothly tapering main pancreatic duct (MPD) is seen entering through the mass rather than “double duct sign” seen in malignancy that involves obstruction and dilatation of both MPD and common bile duct (CBD). CM-FP more commonly is associated with pancreatic parenchymal calcifications and collateral...
duct dilatation. PDACs more commonly show duct dilatation with pancreatic atrophy and increased duct to parenchyma ratio (>0.34), displaced calcifications, vascular involvement, superior mesenteric artery-to-superior mesenteric vein ratio greater than or equal to 1.0, and restricted diffusion on DWI.

9 AIP may show focal, multifocal, or diffuse pancreatic involvement. Focal AIP may mimic PDAC; however, it shows significantly higher CT attenuation values on venous phase than PDACs, delayed enhancement pattern, and significantly lower apparent diffusion coefficient values than in PDAC on DWI. Pancreatic ductal abnormalities like diffuse or segmental narrowing or multiple noncontinuous strictures without marked upstream dilatation and “duct penetrating sign” or “icicle sign” may be seen in AIP. Detection of extrapancreatic manifestations suggesting IgG4-related disease points toward a diagnosis of AIP over PDAC.10,11 Groove pancreatitis presents with the inflammatory process or soft tissue in the pancreaticoduodenal groove (PDG) or involving the pancreatic head that may be associated with medial duodenal wall thickening and enhancement, duodenal luminal narrowing, small cysts in the involved duodenal wall or the PDG, mild smooth tapering of distal CBD and PD, and no vascular involvement.12

**Pancreatic Neuroendocrine Tumors**

Pancreatic neuroendocrine tumors (PNETs) are relatively rare and constitute about 1 to 5% of all pancreatic neoplasms.2 PNETs may be associated with von Hippel-Lindau disease, neurofibromatosis-1, tuberous sclerosis, and multiple endocrine neoplasia type 1 syndrome. According to the World Health Organization classification (2010), NETs are classed as NET G1 (carcinoid, mitotic count <2 per 10 high-power fields (HPF) and/or ≤2% Ki67 index), NET G2 (mitotic count 2–20 per 10 HPF and/or 3–20% Ki67 index), NET G3 (neuroendocrine carcinoma, mitotic count >20 per 10 HPF and/or >20% Ki67 index), and mixed adenoneuroendocrine carcinoma (MANEC). MANECs by definition are those neoplasms in which each component represents >30% of the lesion.13

Well-differentiated NETs are seen as well-defined hypervascular masses that enhance avidly during the arterial phase, enhancing more rapidly and intensely than the normal pancreas. When small (less than 2 cm), they enhance homogenously and typically cause no ductal dilatation or vascular encasement. Larger tumors, however, show heterogeneous enhancement and may cause ductal obstruction and vascular encasement (►Fig. 4).14 PD obstruction in well-differentiated NETs may be seen in serotonin-producing tumors and reflect the local fibrogenic effect of serotonin.15 Poorly differentiated NETs may show ill-defined margins, PD dilatation, and vascular encasement (►Fig. 5). They may sometimes show hypovascular enhancement pattern. Ren et al16 studied differentiating imaging features between hypovascular PNETs and PDACs using contrast-enhanced (CECT). They found that hypovascular-PNETs showed a higher frequency of a well-defined margin and lower frequencies of PD dilatation, local invasion, or metastases as compared to PDAC. The mean attenuation of hypovascular-PNETs at the arterial and portal venous phase and tumor-to-pancreas enhancement ratio was significantly higher than
that of PDAC. The optimal cutoff value of CT attenuation was 50.5 Hounsfield unit (HU) at the arterial phase and 57.5 HU at the portal venous phase. The optimal cutoff value of tumor-to-pancreas enhancement ratio was 0.529 at the arterial phase, and 0.619 at the portal venous phase. Another feature of nonfunctional PNETs is venous tumor thrombus and intraductal growth. Balachandran et al studied incidence of venous tumor thrombus in pancreatic NETs and found venous tumor thrombi in 33% patients.

At MRI, PNETs usually appear hypointense on T1WI and hyperintense on T2WI with respect to the normal pancreas, with enhancement pattern similar to that on CT. Functional imaging contributes in diagnosis and staging of PNETs. Gallium-68 DOTATATE is a form of somatostatin-receptor functional imaging that is usually combined with CT and is used for imaging well-differentiated NETs. 18F-FDG PET is usually used in the assessment of poorly differentiated NETs.

**Pancreatic Lymphoma**

Primary pancreatic lymphoma arising from lymphoid elements in the pancreas is rare, and is defined by following clinical criteria: (1) no evidence of palpable superficial lymphadenopathy; (2) no enlargement of mediastinal nodes; (3) normal leukocyte count; (4) at surgery, the pancreatic mass predominates, with involved lymph nodes confined to the peripancreatic region; and (5) no hepatic or splenic involvement. Pancreatic lymphoma is classified as secondary if there is involvement of lymph nodes except for the peripancreatic nodes or with more than one extranodal site. Lymphomatous involvement of the pancreas calls for nonsurgical management that underlines the necessity to search for secondary signs of lymphoma.

Pancreatic lymphoma shows two morphologic patterns: focal and diffuse form. The focal form commonly occurs in the pancreatic head and typically appears uniformly hypodense at CT and shows minimal enhancement. On MRI, it appears hypointense on T1WI and shows low to intermediate signal intensity on T2WI, and shows mild contrast enhancement. The diffuse form (Fig. 6) presents with generalized homogenous pancreatic enlargement and loss of normal pancreatic lobulations leading to sausage-shaped pancreas. This appearance mimics AIP. This form shows low signal intensity on T1- and T2-weighted MRIs and usually shows mild homogeneous contrast enhancement. PD or CBD dilation or peripancreatic vessel invasion is not a common feature of lymphoma; however, it may encase the peripancreatic vessels.
Cystic Pancreatic Tumors

Serous Cystadenomas

Serous cystadenomas typically present with three morphologic patterns: polycystic, honeycomb, and oligocystic, commonly in middle aged to elderly females in the pancreatic head.\(^{22}\) Polycystic pattern (Fig. 7) presents as a lobulated cystic lesion that consists of multiple (usually more than 6) microcysts measuring 2 cm or smaller that are separated by fibrous septa that may enhance. A fibrous central scar that may show stellate calcification is seen in approximately 30% of the cases. The honeycomb pattern (Fig. 8) presents as numerous subcentimeter cysts that cannot be individually distinguished on cross-sectional imaging. It appears as a well-circumscribed lesion with soft-tissue or mixed attenuation and a sharp interface with vascular structures on CT. MRI can aid in these cases by identifying the cystic nature of the tumor on T2WIs and demonstrate the thin internal septations. The oligocystic (or macrocystic) pattern is uncommon and shows fewer large (> 2 cm) cysts that mimic other cystic tumors such as mucinous cystic neoplasms or intraductal papillary mucinous neoplasm (IPMN). CT findings that are helpful to differentiate these from other oligocystic pancreatic lesions include location of serous cystadenoma in the pancreatic head, its lobulated contours, and the absence of wall enhancement.\(^{23}\) Giant serous cystadenoma, defined as multicystic tumor larger than 10 cm in diameter,\(^{24}\) may present with complications like rupture, obstructive chronic pancreatitis, invasion, or compression of adjacent structures. Serous cystadenoma may present with intratumoral hemorrhage that may closely resemble solid pseudopapillary tumor (SPT); however, the latter presents in younger women and shows features such as a thick wall and solid components. Serous cystadenomas are common in von Hippel-Lindau disease that shows presence of disseminated forms of serous cystadenomas involving the entire pancreas.

Mucinous Tumors

Mucinous tumors are most broadly divided into mucinous cystic neoplasms and IPMN.

Mucinous Cystadenomas

Mucinous cystadenomas are commonly found in middle-aged women, typically in the body or tail of the pancreas. They commonly present as unilocular or mildly septate cystic lesions (multilocular cysts with fewer compartments, usually > 2 cm each) that do not communicate with the pancreatic duct. They are composed of mucinous cysts filled with partially digested acinar cell secretory products that are secreted into the cyst lumen. The cysts may communicate with the pancreatic ductal system or not and may show features such as a thick wall and solid components. CT evaluation of pancreatic neoplasms may aid in identifying these tumors by their characteristic imaging features.
ductal system. The wall of the cyst is thick and shows delayed enhancement (Fig. 9). The lesion may show mildly thickened, enhancing septations within (Fig. 10). Presence of internal enhancing soft tissue elements is indicative of malignancy. Calcification, when present, is usually peripheral and also highly predictive of malignancy. On MRI, the lesion commonly appears hypointense on T1WI and hyperintense on T2WI, despite the cyst fluid being mucin filled. Mildly increased T1 signal intensity of the fluid in mucin-containing cysts also may be seen.

**Intraductal Papillary Mucinous Neoplasm**

IPMNs were first described by Ohhashi in 1982 and classified by the World Health Organization as a distinct histological type of exocrine tumor of the pancreas in 1996. In 2010, IPMN was further subcategorized according to its malignant transformation into IPMN with low or intermediate dysplasia, IPMN with high-grade dysplasia, and IPMN with invasive cancer.27,28

IPMN is characterized by cystic dilation of the main or branch PD due to papillary growth and excessive mucin production within the PD system that are classified as main-duct (MD)–IPMN and branch-duct (BD)–IPMN, respectively.29

- **MD-IPMN:** It can have either segmental or diffuse dilatation of the MD, without any obvious cause for obstruction.
- **BD-IPMN:** Cystic tumor along the branches of the PD, with communication with the PD. MPD appears normal (Fig. 11).

Few cases of IPMN have been described that were associated with extrapancreatic mucin, with development of pseudomyxoma peritonei after presumed mucin leakage.30

**Adenocarcinoma Arising in IPMN**

Invasive cancer arising from IPMN has distinctive radiologic appearances (Fig. 12); risk of malignancy is significantly higher in MD-IPMNs than BD-IPMN.29 According to the 2012 international consensus guidelines, a MPD size larger than 10 mm, enhancing mural nodule, and jaundice associated with a cystic mass in pancreatic head were stated as “high risk stigmata.” MPD of size 6 to 9 mm, nonenhancing mural nodule, MPD stenosis with parenchyma atrophy, cyst size \( \geq 3 \) cm, and thickened and enhancing cyst wall are stated as “worrisome features.”31

**Solid Pseudopapillary Tumor**

SPT commonly occurs in women in the second to fourth decade with the most common location being the tail of pancreas.32,33 SPT is generally large well-encapsulated mass with varying solid and cystic components caused by hemorrhagic degeneration. Calcifications and heterogeneously enhancing solid areas may be present at the
periphery of the mass, which are iso- to hypoattenuating to the normal pancreatic parenchyma on arterial and venous phase (►Fig. 13).

MRI typically shows a well-defined lesion with a mix of high and low signal intensity on T1WI and T2WI, representing blood products. T2WIs show a thick fibrous capsule, which is seen as a discontinuous rim of low signal intensity. DCE-MRI shows early peripheral heterogeneous enhancement of the solid portion with progressive fill-in. SPT may show atypical features in the form of origin in the head of pancreas, PD obstruction and resultant pancreatitis, adjacent structure invasion, and liver metastases. SPT may also show imaging features such as hypervascularity, cystic change, and a well-defined border without desmoplastic reaction mimicking islet cell tumor. SPT may sometimes show central, stippled, or eggshell calcifications.
Pancreatic Metastases
Primary neoplasms that can commonly metastasize to pancreas are renal cell carcinoma, lung, breast, malignant melanoma, carcinoma of gastrointestinal origin, and prostate cancer. Hiotis et al. found renal cell carcinoma to be the most frequent primary neoplasm (62%) metastasizing to pancreas. Three patterns of metastatic involvement of the pancreas are solitary metastasis, multiple small nodules, particularly with absence of vessel infiltration and/or PD involvement. Radiological appearance of the metastases depends on the type of the primary tumor. They appear as well-circumscribed hypodense lesions on CT that are usually hypoattenuated compared to normal gland tissue on T1WI, heterogeneous or moderately hyperintense on T2WI and show similar enhancement pattern on DCE-MRI as on CECT.

Conclusion
Pancreatic malignancies are a common occurrence. Radiology plays a pivotal role in diagnosis and staging of the disease. Hence, radiologists should be aware of the uncommon presentations of common pancreatic malignancies, and common presentations of uncommon pancreatic malignancies.

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Conflicts of Interest
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