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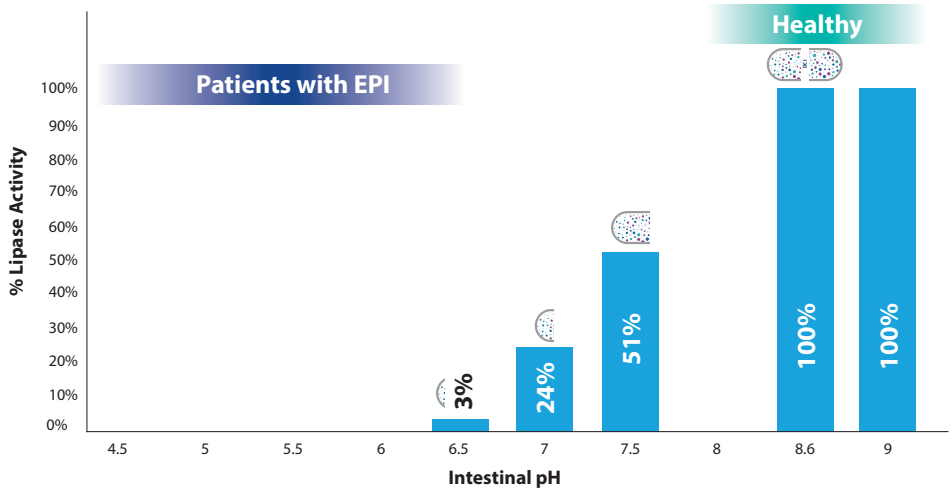
The Difference of Bicarbonate for the treatment of EPI

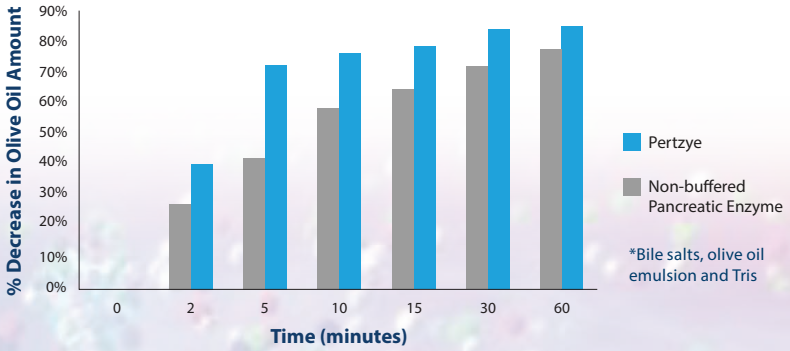
Patients with EPI have lower duodenal pH than healthy individuals, which could result in lipase being less active

The most common adverse reactions (≥ 10%) are: diarrhea, dyspepsia, and cough.



In a simulated environment with a pH of 7, Pertzye breaks down more emulsified fat compared to non-bicarbonate buffered Pancreatic Enzyme[1]

% Decrease in Olive Oil Over Time for Pertzye vs. Non-buffered Pancrelipase in Emulsion Substrate*



*Bile salts, olive oil emulsion and Tris

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Pertzye® (pancrelipase) is indicated for the treatment of exocrine pancreatic insufficiency in adult and pediatric patients.

Important Safety Information

- Fibrosing Colonopathy is associated with high doses, usually over prolonged use and in pediatric patients with cystic fibrosis. Colonic stricture reported in pediatric patients less than 12 years of age with dosages exceeding 6,000 lipase units/kg/meal. Monitor during treatment for progression of preexisting disease. Do not exceed the recommended dosage, unless clinically indicated.
- Irritation of the Oral Mucosa may occur due to loss of protective enteric coating on the capsule contents. Do not crush or chew PERTZYE capsules or capsule contents.
- Hyperuricemia has been reported with high dosages, consider monitoring blood uric acid levels in patients with gout, renal impairment, or hyperuricemia.
- Risk of Viral Transmission: The presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.
- Hypersensitivity Reactions: Monitor patients with known reactions to proteins of porcine origin. If symptoms occur, initiate appropriate medical management; consider the risks and benefits of continued treatment.
- The most common adverse reactions (≥ 10%) are: diarrhea, dyspepsia, and cough.
- Do not substitute other pancreatic enzyme products for PERTZYE.

Please see Full Prescribing Information at www.pertzye.com.

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SMART Topic

CT Images of the Pancreas for Beginners

Yusuf Baytar MD[1], David C Whitcomb MD PhD[2], Anil K Dasyam MD[1]

1. *Abdominal Imaging Division, Department of Radiology, University of Pittsburgh, Pittsburgh, PA, USA.*
2. *Department of Medicine – emeritus, University of Pittsburgh, Pittsburgh, PA, USA.*

1. Overview

Imaging is critical to determining the etiology and progression of pancreatic diseases. The most commonly utilized modality is computed tomography (CT), typically, contrast enhanced CT (CECT). Here we present a primer for health care providers on the evaluation of a normal triphasic pancreas imaging (pancreas protocol CT), and examples of end-stage disease. Compared to normal, we provide images of an atrophic pancreas, advanced chronic pancreatitis (CP), residual pancreas post Whipple procedure and fatty pancreas. Each image is described in a systematic way with a brief differential diagnosis.

2. Background

Diagnosis of pancreatic disease through most of the 20th century relied on abdominal X-rays, with or without oral contrast. The diagnosis of chronic pancreatitis (CP) required the triad of dense calcifications in the area of the pancreas on X-ray, steatorrhea (oil in the stools) and diabetes mellitus (DM). Pancreatic cancer was diagnosed by a large mass in the pancreas that distorted the contour of the stomach and duodenum on barium studies, accompanied by painless jaundice from obstruction of the common bile duct in the pancreatic head and confirmed with exploratory surgery. The problem here is that these diagnostic definitions could only be established in late-stage disease that was irreversible and devastating. Other techniques such as angiograms and early transabdominal ultrasound were invasive, of limited accuracy and also detected late disease.(1)

Early CT scans were revolutionary, but the images were of low resolution and lacked information about dynamic processes. Continual innovation in CT scanners and software allow pancreatic pathology to be detected at early stages, especially within a compelling clinical context.

The focus of this paper is not on early detection, but rather a primer on the features of CT in a normal pancreas and end stage diseases with multiple abnormal features.

3. Normal Triphase CECT Scan

Figure 1 illustrates a normal pancreas before contrast (1a), 35-45 seconds post intravenous (IV) contrast injection to capture the late arterial phase or pancreas phase(1b), and 60-70 seconds post-injection to capture the portal-venous stage.

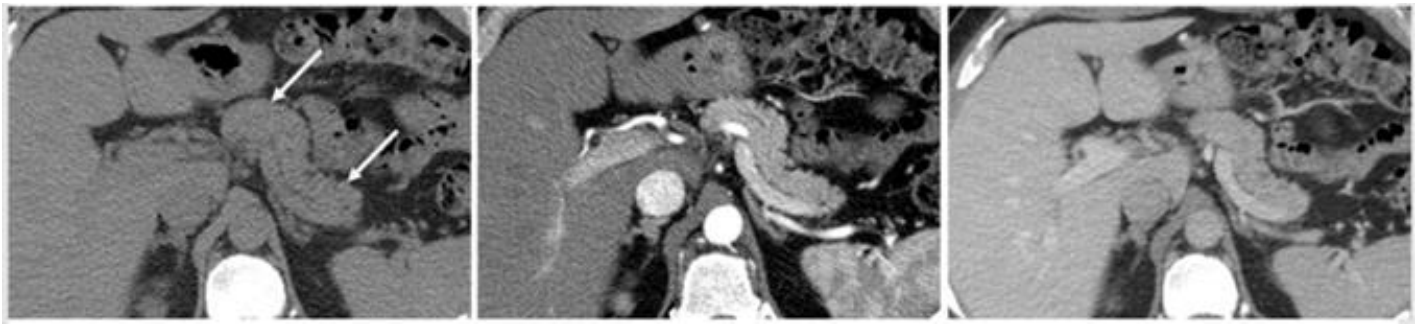

Figure 1. Triphasic CECT Scan using the pancreas protocol. Unenhanced phase (1a.) The pancreas is in the center of the image (white arrows) extending laterally towards the spleen. Post-contrast pancreas phase (1b.) There is homogeneous marked enhancement of the pancreas which is brighter than surrounding organs and the splenic vein runs immediately dorsal to the pancreas. The post-contrast portal venous phase image (1c.) In addition, the venous phase provides information on status of liver and rest of the abdomen for metastasis or other complications.

Abbreviations used in this paper: CT, computed tomography; CECT, contrast enhanced CT; CP, chronic pancreatitis; DM, diabetes mellitus; IV, intravenous; EPI, pancreatic exocrine insufficiency; IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; CF, cystic fibrosis; CEL, carboxyl ester lipase; AP, acute pancreatitis; EUS, endoscopic ultrasound; PCCT, photon counting CT; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

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Key feature of a normal pancreas

- The pancreas has a uniform, smooth to slightly lobulated contour.
- The size of the pancreas varies depending on age and gender, with an anteroposterior dimension typically greater than 20 mm in adults, which markedly decreases after the eighth decade as part of the normal aging process. (Wang, 2019 #9113)
- The pancreatic duct is visible but smooth and of small caliber (<3 mm in the head, <2 mm in the tail – may be slightly larger in older individuals)
- There are no calcifications, masses or cystic lesions on the pre-infusion CT phase.
- There are no masses or lesions that are distinguished by a discrete focus of increased or decreased contrast enhancement compared to the rest of the organ.

A full evaluation of the pancreas requires review of all axial images of the upper abdomen as well as multiplanar reconstructions when appropriate.

Considerations of radiologist

Abdominal radiologists often use a systematic approach in evaluating pancreas. This includes assessment of pancreatic parenchyma, the pancreatic duct, peripancreatic fat and the peripancreatic vasculature and organs. The pancreatic parenchyma is evaluated for enhancement characteristics, focal lesions, calcifications and size (atrophy or enlargement). The pancreatic duct is evaluated for course, strictures/obstruction, dilation and intraluminal stones. The peripancreatic fat is evaluated for presence of any stranding or collections. The peripancreatic vessels are assessed for patency, stenosis, aneurysms or thrombosis/occlusion.

4. Atrophic Pancreas

Figure 2 illustrates the non-contrast CT image of an individual with an atrophic pancreas. Compared to a normal pancreas (Fig. 1a) the pancreas is seen as a thin ribbon immediately anterior to the splenic vein.

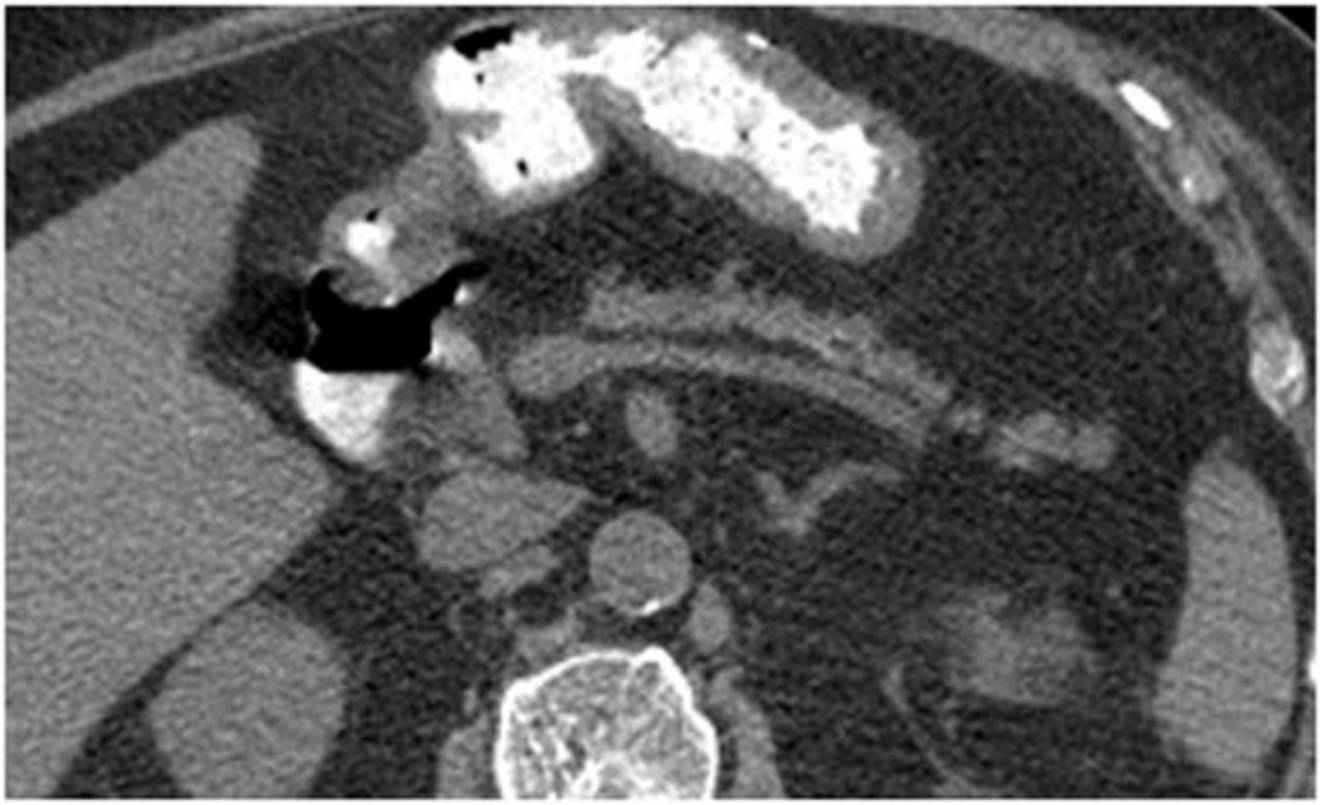

Figure 2. Pancreatic atrophy. Unenhanced axial CT image through the body and the tail of the pancreas showing diffuse decrease in thickness of the parenchyma.

Key Features of an atrophic pancreas

- The pancreatic thickness varies with age and generally ranges from 14 to 21mm.
- There may be an abrupt transition between normal and atrophic pancreas due to a pancreatic ductal stricture (e.g. from previous trauma), or obstructing mass.
- The size of the duct may be large or small. This may correlate with the etiology.

Atrophy of the pancreas from any cause reduces pancreatic exocrine mass that synthesizes and secretes pancreatic digestive enzymes. Clinical features reflect pancreatic exocrine insufficiency (EPI) and maldigestion. Most importantly, this leads to deficiency of fat-soluble vitamins as

the pancreas is the only significant source of lipases to digest dietary fats. The pancreas is also important for producing R factor, critical for vitamin B12 absorption.

Differential diagnosis of pancreatic atrophy

- Chronic pancreatitis.
- Sequela of autoimmune pancreatitis
- Old age (senile chronic pancreatitis)
- Long-standing type 1 DM (see review by Haberl & Virostko[2])
- Pancreatic duct obstruction from tumors in the head of the pancreas
- Pancreatic duct obstruction from main-duct intraductal papillary mucinous neoplasm (IPMN), with enlarged duct and parenchymal atrophy.
- Main duct obstruction from strictures or pancreatic stones.
- Severe malnutrition

Considerations of radiologist

The clinical history provides important context for the evaluation of CT scan by radiologists. In the case of pancreatic atrophy, the radiologist evaluates pancreas for presence and subjective severity of atrophy. The images are also scrutinized for any identifiable etiology such as pancreatic ductal stricture or an obstructing mass. Etiology is sometimes apparent on evaluation of prior exams. For example, autoimmune pancreatitis or recurrent acute pancreatitis may be evident on prior imaging studies while atrophy may be the sole manifestation on current exam.

5. Chronic Pancreatitis

Figure 3 illustrates end-stage CP with intraductal calculi, calcifications, dilated main pancreatic duct and parenchymal atrophy. Other common features include pseudocyst, splenic vein thrombosis – often associated with gastric varices and phlegmonous peripancreatic masses.

The definition of CP and a progressive model has been adopted world-wide that provides clarity on both the variability in clinical features and the opportunity to diagnose CP in contrast to other disorders in the differential diagnosis.[3] Clinical features include variable degrees of fibrosis, abdominal pain, EPI, DM, maldigestion, malnutrition, weight loss and increased risk of pancreatic ductal adenocarcinoma. Challenges in the early diagnosis of CP have been defined.[4] The etiologies contributing to CP is given in the TIGAR-O list.[5] Early chronic pancreatitis lacks advanced clinical and imaging features and results in diagnostic challenges. See review for diagnosis of CP (Yadav and Whitcomb)[6].

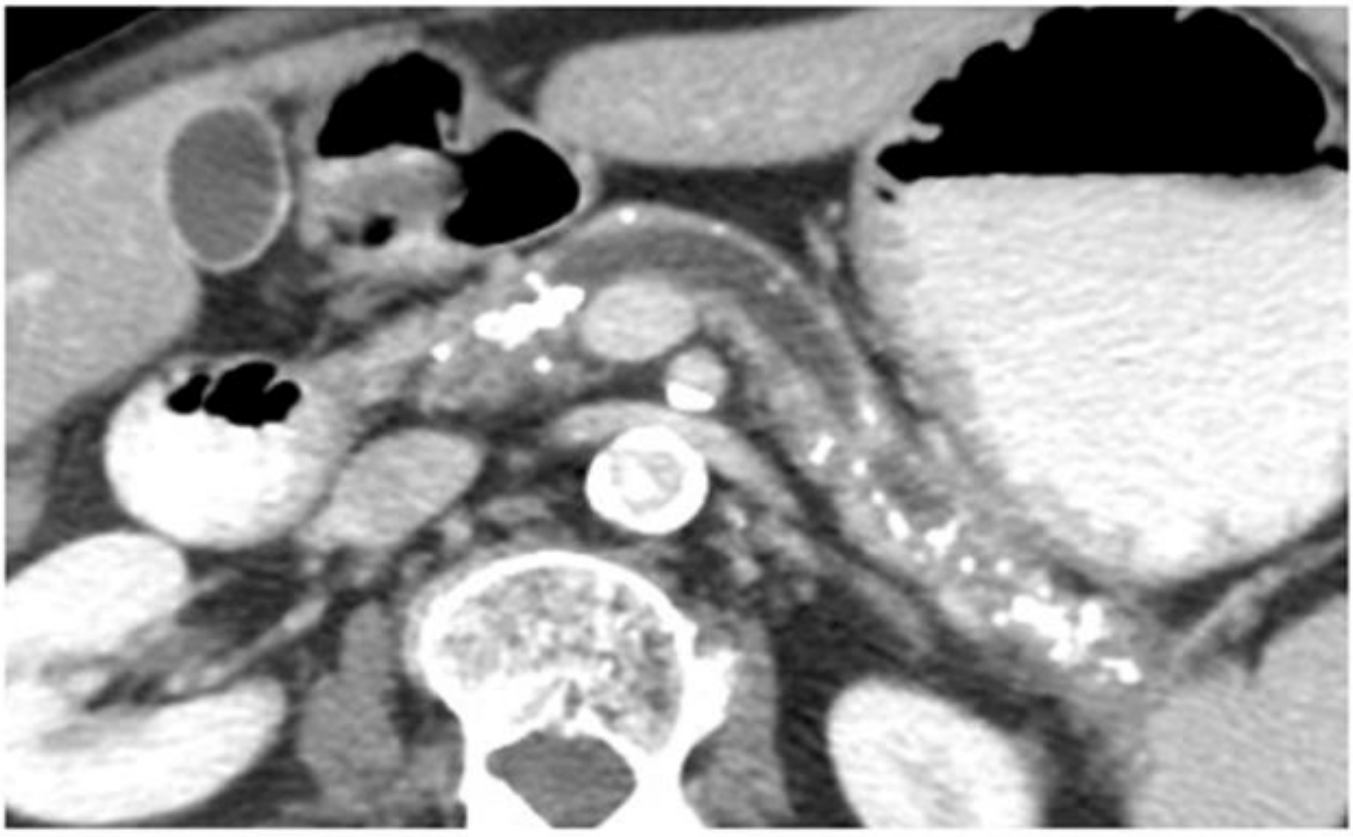

Figure 3. Chronic pancreatitis. Key features include parenchymal calcifications, intraductal calculi, dilated main pancreatic and loss of pancreatic parenchyma (atrophy).

For a method to quantify progressive pancreatic features in CP see Dasyam et al.[7] A consensus statement aimed at standardizing the reporting of CP on CT and MRI/MRCP has also been developed, incorporating both pancreatic ductal and parenchymal changes into the assessment of disease severity. {Tirkes, 2019 #6519}

6. Post Whipple pancreas

The classic Whipple operations is used to describe a pancreaticoduodenectomy. The key components include resection of the head of the pancreas with the antrum of the stomach, the duodenum and the distal common bile duct. The surgeon then brings the mid-jejunum up to the bottom of the stomach where an anastomosis is made for the food to go down the efferent limb. The afferent limb of jejunum (upstream of the gastrojejunal anastomosis) is then attached to the common bile duct (choledochojejunostomy) and the pancreatic duct (pancreato-jejunostomy).

The pylorus-preserving Whipple is used, when possible (e.g. no tumor involvement), where the duodenum is divided distal to the pylorus, and the jejunum is attached to the duodenal stump just distal to the pylorus.

Other operations can be used to remove the head of the pancreas, such as a duodenum-preserving pancreatic head resection. This type of surgery is usually reserved for benign conditions such as an inflammatory mass in the head of the pancreas due to chronic pancreatitis.

Common indications for a Whipple include malignant tumors of the head of the pancreas (e.g. pancreatic ductal adenocarcinoma, or PDAC), ampullary cancers, bile duct cancers, some duodenal cancers, chronic pancreatitis complications such as obstructing masses or intractable pain. Review of the past medical history typically provides the indication for the individual patient.

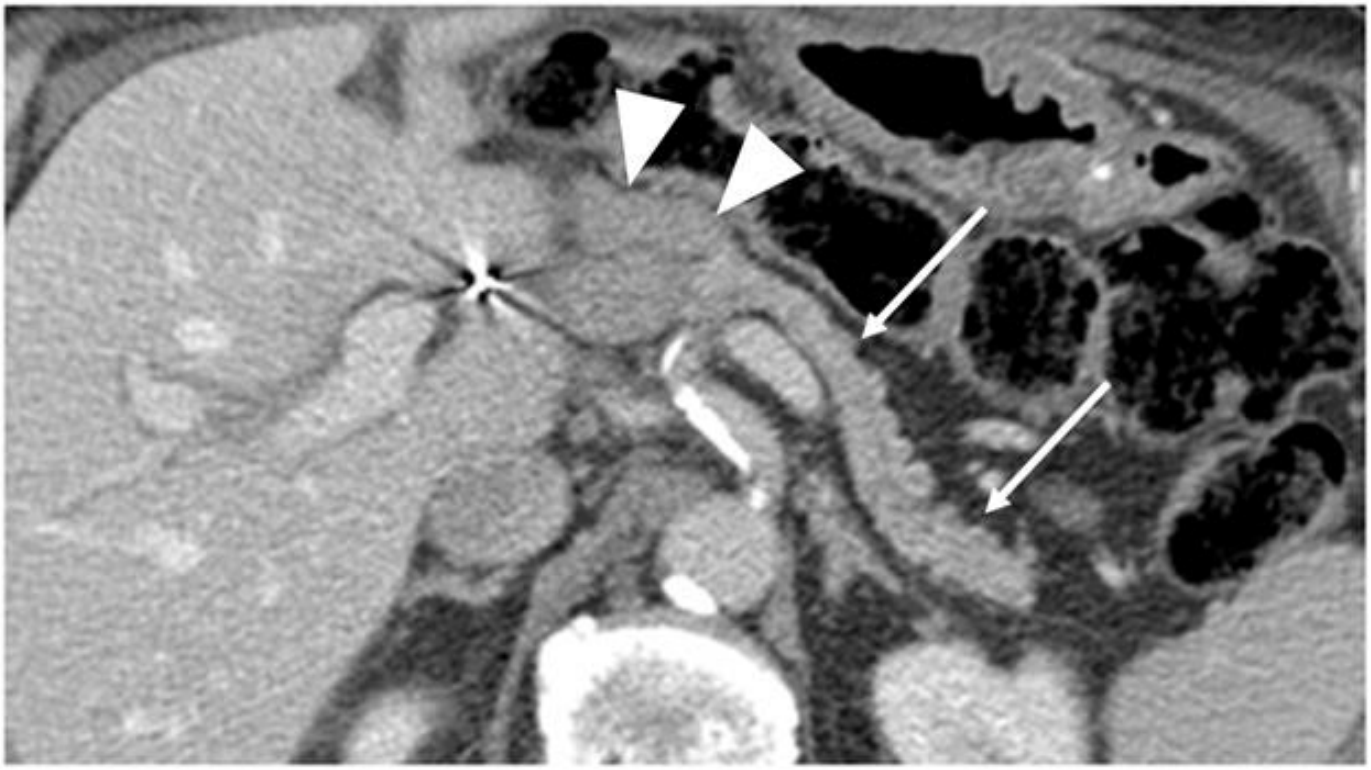

Figure 4. Pancreas Post Whipple. The residual pancreas (white arrows) is anastomosed to pancreatobiliary limb of jejunum (white arrowheads).

Key Imaging Features of a post-Whipple pancreas

- Absence of the head of the pancreas.
- Absence of the duodenum.
- A blind ending jejunal loop (pancreaticobiliary/afferent limb) connected to the remnant pancreas and to the common bile duct via two separate anastomoses.
- An anastomosis between the stomach and a loop of jejunum.

Considerations of radiologist

The indication for a Whipple is important for the radiologist in reviewing abdominal imaging studies. If the procedure was done for PDAC in the early postsurgical setting CT scan can be obtained to rule out collections and leak. Fluid and stranding in the surgical bed are common findings in the perioperative setting. The first postoperative restaging scan serves as the baseline and should demonstrate regression or stability of the expected early postoperative findings. Collapsed jejunal segment near the pancreatico-jejunostomy should not be misinterpreted as tumor recurrence. Although a focal soft tissue density or mass should raise concern for recurrence, mild induration at the surgical bed and crescentic soft tissue posterior to the SMV and SMA often reflects postoperative fibrosis

which may persist indefinitely. Reactive nodes are also common in the root of mesentery but usually resolve within 3–6 months. Essentially, findings should be carefully compared to the prior studies and progressive findings should raise high concern for neoplastic processes.[8]

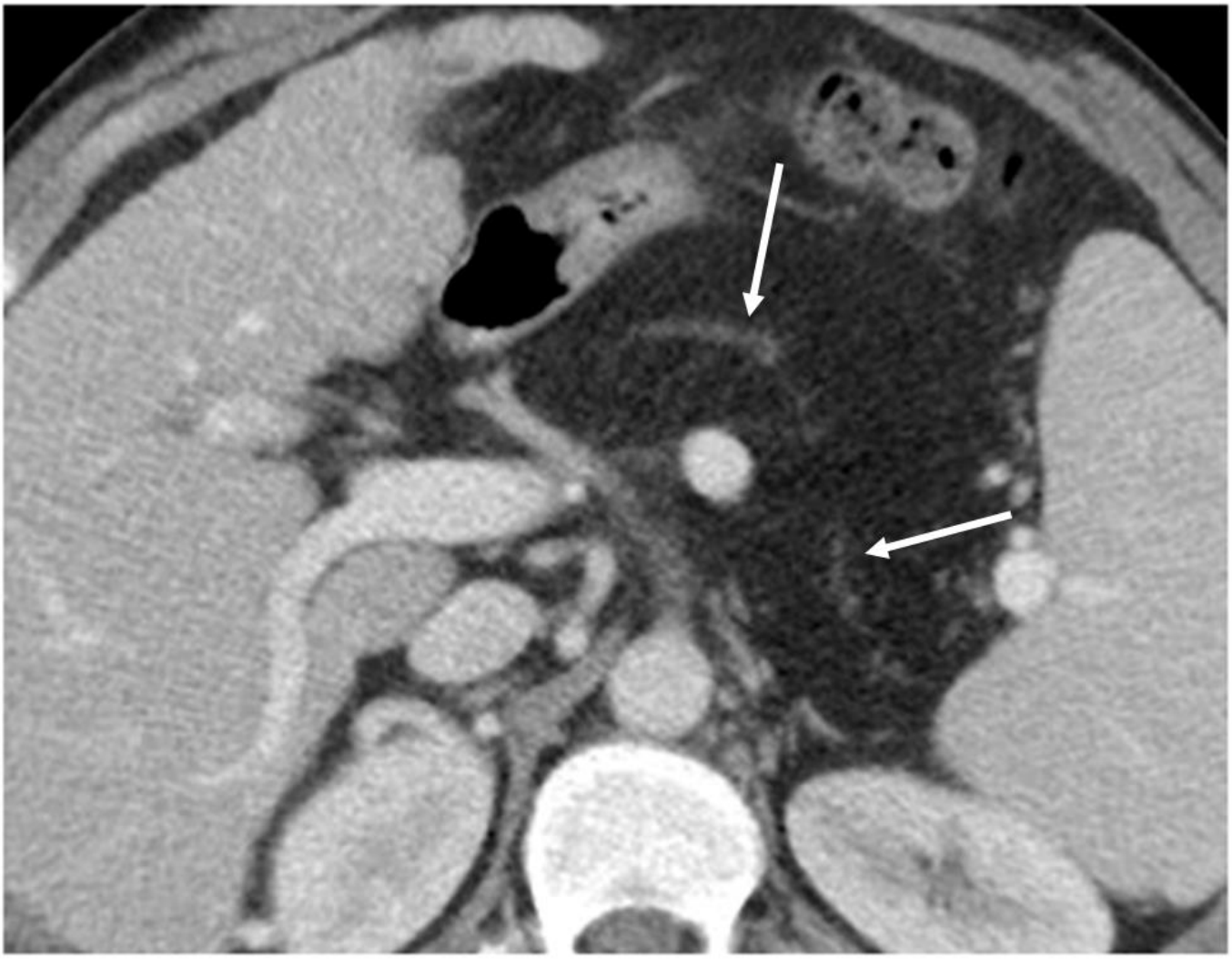

Figure 5. Fatty pancreas. Note the pancreatic duct (white arrows) running through the pancreas which is completely replaced by fat which is low in attenuation.

7. Fatty pancreas

Figure 5 illustrates fatty pancreas. The CT image may be striking as increased pancreatic fat results in decreased attenuation through the pancreas. Compared to the spleen, for example.[9]

Fatty pancreas is more common than initially thought being present in nearly 18% of individuals in the UK Biobank.[10] It is more common in patients with acute pancreatitis, CP and DM, and is associated with PDAC[10, 11] (possibly through shared etiologies linked to inflammation).

The etiology of fatty pancreas cannot be determined by CT scan. In some cases, there is infiltration of fat cells – adipocytes – into the pancreatic lobules, replacing or intermingling with acinar cells which occurs with diabetes, metabolic syndrome and conditions with parenchymal stress such as genetic disorders. In addition, there can be a buildup of adipocytes in the connective tissue between lobules, especially in older individuals. While it is possible that acinar cells dedifferentiation to become fat containing cells, the frequency and importance of this mechanism remains unproven.

There are many conditions associated with fatty pancreas with the most common being obesity, fatty liver (steatosis), and chronic inflammation (see list from Majumder et al Table 1[9]) In addition, there may be polygenic risk factors increasing likelihood of fatty pancreas and contributing to the high frequency of fatty pancreas in some populations.[12]

Figure 5 is fatty pancreas from a patient with cystic fibrosis, (CF) and represents the most common pancreatic imaging find in these patients. In CF and other genetic disorders of the pancreas such as some carboxyl ester lipase (CEL) gene mutations[13] there is chronic inflammation – often without acute pancreatitis (AP) resulting in loss of

acinar cells and replacement with adipocytes rather that fibrosis.

Key Imaging Features of fatty pancreas

- Fatty pancreas is assessed better in non-contrast CT scans.
- On CECT, when fat infiltration is interspersed with the normal enhancing pancreas, the fat regions remain hypodense resulting in a mottled appearance.
- When pancreas is diffusely replaced by fat, pancreatic parenchyma appears hypodense (low attenuation) compared to normal pancreatic tissue or surrounding organs such as the spleen.
- Preserved pancreatic contour with minimal volume loss.
- In some cases where fat infiltration is focal, (such as risk staging or suspicion of a tumor) further evaluation should be done using MRI or endoscopic ultrasound (EUS).[14]

Considerations of radiologist

The increasing recognition among clinicians that fatty pancreas may be either a biomarker of pancreatic disease or a risk factor for AP, CP, DM and PDAC is important because the finding may have clinical implications rather than just an incidental finding. Radiologists assess pancreas for presence, distribution and severity of fat infiltration. When focal, fat infiltration may mimic malignancy. MRI is superior to CT in distinguishing focal filtration from tumor.

8. Future Directions

Although the pancreas protocol CT currently is the modality of choice for assessment of the pancreas in various indications; the photon counting CT (PCCT) which came into clinical use in 2021 has been shown to be promising for substituting the former with its higher spatial resolution and decreased image noise that enable more detailed visualization of the pancreas including the neural, lymphatic, vascular and ductal structures. Another advantage is that it gives less radiation to the patient. Preliminary studies have shown that PCCT provides more detailed evaluation of the pancreatic duct than MRCP and enhances detection of the PDAC which occasionally is subtle and poorly discernible from the gland and enhances accuracy in evaluation of the tumoral vascular involvement and resectability.[15]

9. Conclusions

Abdominal imaging remains a key medical tool in disease detection, diagnosis and staging. CT scan is often the initial imaging method with incidental finding of pancreatic disease, verification of clinical suspicions or monitoring disease progression.

This primer highlights the normal appearance of the pancreas as well as 4 common conditions that may be encountered in clinical practice. It is designed to provide an introductory overview of how CT scans that include the pancreas are approached and read by experienced radiologist. It is not comprehensive (e.g. it does not cover acute pancreatitis, cysts, tumors, etc.) and only provides introductory considerations.

As technology and computational approaches continue to advance, CT and other imaging modalities will continue to evolve into more power and useful clinical tools to help early detection of disease and monitor the effectiveness of precision interventions.

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Corresponding Author

Yusuf Baytar MD
Department of Radiology
203 Lothrop Street
EEI Suite 700
Pittsburgh, PA 15213, U.S.A.
baytary@upmc.edu

Author Contributions

AKD and DCW concept, DCW first draft. All authors developed the paper and approved the final draft.

Conflicts of Interest

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