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Imaging Diagnostics in Pancreatic Cancer

A Clinical Guide

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To my dear and loving wife Anu, my daughter Arya, my son Arjun, and my parents Vinod and Kamlesh Anand, without whose love, dedication, and sacrifice, nothing in my life would be possible. I am forever grateful and blessed to have you all in my life. Everything that I am, I am because of you.

Preface

It is with great pleasure that we present *Imaging Diagnostics in Pancreatic Cancer*. The role of diagnostic imaging in the management of pancreatic cancer has evolved over the years with advancements in technology in both radiographic and endoscopic imaging techniques. The purpose of this textbook is to provide a comprehensive, state-of-the-art review of how various imaging modalities impact the management of pancreatic cancer, from a multidisciplinary perspective. This text is therefore meant to serve as a valuable resource for gastroenterologists, medical oncologists, surgical oncologists, radiologists, radiation oncologists, medical students, fellows and residents in training, and researchers with an interest in pancreatic cancer. We will review imaging modalities used in the diagnosis, staging, and management of pancreatic cancer; recent advances in endoscopic ultrasound (EUS) such as contrast-enhanced endoscopic ultrasound and real-time elastography; staging characteristics utilized by medical and surgical oncologists in deciding on appropriate treatment options for pancreatic cancer, and summarize available data on the use of imaging modalities in the screening of pancreatic cancer and who should be screened. A review on the use of radiation therapy for pancreatic cancer will also be discussed as well as when fiducial placement should be considered in targeting a malignancy to help guide radiation therapy.

This textbook is meant to serve as a useful resource for physicians and researchers dealing with, and interested in, this challenging malignancy. We believe this text will provide a concise, yet comprehensive, summary of the current use of diagnostic and therapeutic imaging techniques and procedures in the management of patients with pancreatic cancer and hopefully stimulate future investigative efforts. Multidisciplinary care is an integral part of the management of pancreatic cancer. This is why we chose to take the unique approach of including collaborating authors from a variety of integrated disciplines, including radiology, gastroenterology, and medical, surgical, and radiation oncology, from large tertiary academic centers, cancer centers, and local community hospitals. Such an approach will allow the reader to see how this challenging disease is managed from different clinical perspectives, regardless of the clinical setting.

I have been very fortunate to have had the opportunity to work with and be mentored by these experts. I'd like to thank my co-editor and mentor, Dr. Peter Darwin, and all the authors for their tireless work in putting this project together. A tremendous amount of effort on the part of each individual author has led to the text you now hold in your hands. Without them, this project would not have been possible. Dr. Darwin and I are deeply grateful to them for their outstanding collaboration.

Norwalk, CT, USA Naveen Anand

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Part I
Imaging Modalities Used in the Diagnosis and Staging of Pancreatic Cancer

Chapter 1
Multi-detector CT Scan

Ronald P. Lee, Dugho Jin, and Tiffany Han

Introduction

In 2020, pancreatic cancer is projected to be the tenth most common cause of cancer, but accounts for the third most common cause of all cancer-related deaths in the United States. The incidence of pancreatic cancer continues to rise [1], and unfortunately this remains a lethal disease. The 5-year survival rate has improved but only marginally over the years, from approximately 3% in the 1970s to an overall 5-year survival rate for all stages of approximately 9%. If the cancer is localized, confined to the pancreas, surgery is the best curative option, with a reported 5-year survival rate of up to 37%. The 5-year survival for regional disease, extending beyond the pancreas into the surrounding organs or lymph nodes, decreases to 12%. The 5-year survival for metastatic pancreatic cancer is a dismal 3% [2]. Therefore, detection of the tumor at an early stage allows for improved survival rates [3, 4]. However, the vast majority of patients presenting with pancreatic cancer are not surgical candidates for the resection of pancreatic cancer, due to metastatic spread. The majority of pancreatic cancers are exocrine adenocarcinomas, 93% [5]. Therefore, this chapter will discuss the imaging of pancreatic adenocarcinomas with multi-detector CT scan.

Only 20–30% of newly diagnosed pancreatic adenocarcinoma patients are surgical candidates. Surgical resection with curative intent has a high rate of recurrence, especially patients with positive surgical resection margins. Surgery offers the pancreatic adenocarcinoma patients the only opportunity for cure, but many patients are not eligible for primary resection due to advanced disease at the time of diagnosis. New treatment regimens in the management of non-metastatic pancreatic cancer now include upfront neoadjuvant chemotherapy or chemotherapy and radiation

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therapy to help achieve negative resection margins. Therefore, the goal of administering neoadjuvant chemotherapy is for curative resection and negative resection margins or to downgrade a locally advanced pancreatic tumor [6]. Based upon the current National Comprehensive Cancer Network (NCCN) guidelines, the goal is to optimize the staging of pancreatic cancer to achieve a curative surgical resection with R0 margin negative surgical results, while minimizing the surgical morbidity and risk of tumor recurrence. Imaging plays a critical role in the appropriate stratification of patients into the R0 (no residual disease) or R1 (residual microscopic disease) category versus R2 resections (macroscopic disease). R2 resection patients have a poor surgical outcome and do not benefit from surgical resection. The NCCN clinical practice guidelines recommend a multidisciplinary approach when reviewing imaging and evaluating patients with pancreatic cancer for resectability [4, 52]. Thus, radiology plays a critical role in the multidisciplinary management of patients with pancreatic cancer and in the assessment of treatment options.

CT Imaging

CT scan is the primary imaging modality in the initial assessment of patients for the detection and staging of pancreatic adenocarcinoma and other pancreatic neoplasms. The multi-detector CT is extremely fast, able to scan the abdomen and pelvis in seconds, and provides high-resolution isotropic images. CT is also central to the management and monitoring of pancreatic cancer. According to the most recent 2020 NCCN guidelines for patients with a clinical suspicion of pancreatic cancer or evidence of a dilated pancreatic and/or bile duct, a pancreatic protocol dual-phase CT is the primary imaging modality of choice [7]. The US Preventive Services Task Force continues to recommend against screening asymptomatic patients for pancreatic cancer [8]. However, there are investigational studies underway to determine if screening high-risk patients with strong family histories of pancreatic cancer, genetic risk factors, or new onset diabetic patients may prove useful [4].

Imaging of the pancreas allows for the direct visualization and detection of the pancreatic primary neoplasm. Cross-sectional imaging can effectively stage the pancreatic carcinoma and search for evidence of vascular invasion, lymphadenopathy, peritoneal carcinomatosis, and liver metastases. Therefore, CT evaluation can accurately stage a patient with pancreatic adenocarcinoma and determine resectability [9].

The detection of a small pancreatic adenocarcinoma can be challenging. Small pancreatic neoplasms may be difficult to visualize, especially the isoattenuating lesions and lesions that do not produce a contour deformity or pancreatic ductal dilation. The CT sensitivity and specificity for the detection of pancreatic adenocarcinoma has improved with each technical advancement in multi-detector CT scanner technology and the use of dual-phase imaging during the injection of intravenous contrast.

CT radiographic signs for the diagnosis of pancreatic adenocarcinoma are focal areas of low attenuation and change in texture at the site of an abrupt pancreatic or common bile duct caliber change. Pancreatic adenocarcinomas tend to enhance less than the normal pancreatic tissue. Focal hyper-attenuation and contour abnormality are also seen [10]. The detection of the pancreatic neoplasm is based upon the observed differences in the CT density of the pancreatic cancer relative to the normal pancreatic parenchyma. Therefore, the goal of intravenous contrast timing in CT imaging is to optimize the timing for peak pancreatic gland enhancement, with the pancreatic adenocarcinoma appearing as a low-density lesion within the background of normal enhancing pancreatic parenchyma.

The CT modality is preferred for the initial staging of pancreatic ductal adenocarcinoma due to the high spatial resolution, availability of the modality, fast speed of imaging, and lower cost than MRI. Intravenous iodinated contrast is required to increase contrast resolution, but intravenous contrast may not be administered in patients with poor renal function or severe contrast allergies. MRI offers high-contrast resolution for pancreatic cystic lesions and may be an adjunct to pancreatic tumors that are difficult to visualize by CT. It may also be performed in patients with an allergy to iodinated contrast. In addition, it provides improved characterization of liver metastases. However, MRI is limited by its higher cost, imaging artifact, and longer duration of study and may not be compatible for patients with certain MRI-incompatible implants and patients who are claustrophobic or too large to fit in the scanner. PET CT may play a role in the assessment of metastatic disease [11].

CT Technique

Intravenous administration of contrast medium is required to maximize the differentiation of the normal pancreas from pancreatic neoplasm. Many studies were performed to evaluate the optimal contrast injection techniques and timing of imaging. These studies have determined that higher contrast rate of administration and biphasic post-contrast imaging are ideal for pancreatic cancer assessment.

Early stage small pancreatic carcinomas can be notoriously difficult to visualize. Maximum enhancement of the pancreas is critical in the detection of the pancreatic neoplasm, to provide the highest contrast between the tumor and the pancreatic parenchyma. Peak pancreatic gland enhancement occurs earlier than the optimal portal venous phase of liver enhancement as the arterial supply of the pancreas is via the celiac artery branches (Fig. 1.1a). The time of peak pancreatic enhancement varies with the rate and volume of intravenous iodinated contrast administration [10, 12]. There are many different CT scanning protocol strategies to optimize the phase of imaging, to target maximum arterial phase opacification of the peripancreatic vessels at 18–35-second scan delay, pancreatic parenchyma at 35–45-second scan delay, and portal phase imaging at 60–70-second scan delay. The advancement in CT multi-detector row helical technology allowed for faster volumetric image acquisition during any phase of contrast enhancement. However, the timing and

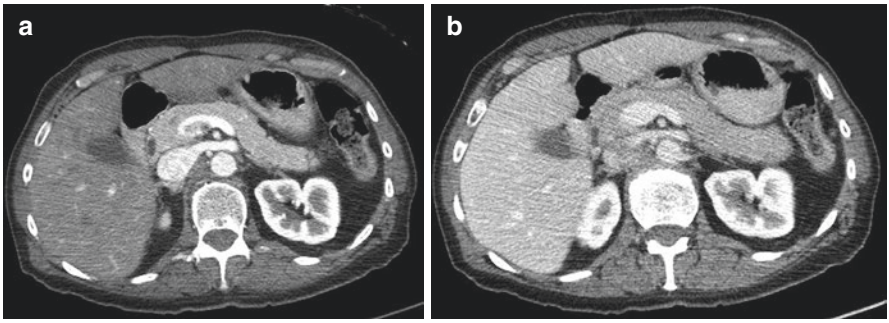

Fig. 1.1 (**a**) Normal arterial phase – fixed 40-second delay from IV contrast administration. (**b**) Normal portal venous phase – fixed 70-second delay from IV contrast administration

phase of imaging with multi-detector CT is critical for optimal pancreatic tumor conspicuity [53].

The portal venous phase of imaging is optimal for the evaluation of liver metastases (Fig. 1.1b). The liver has a dual blood supply via the hepatic artery and the portal vein. As pancreatic adenocarcinoma leads to hypo-vascular tumors and metastases, the optimal phase for liver metastasis evaluation is during the portal venous phase of imaging acquisition. This phase also allows a second look at the pancreatic parenchyma. In addition, assessment of the venous vasculature, especially the portal vein, is critical in the preoperative evaluation of pancreatic malignancies. Venous flow artifacts are eliminated in the portal venous phase, allowing for differentiation of flow artifact from venous thrombus. The other venous vessels, adjacent organ systems, bowel, and lymph node status can be accurately viewed during this phase.

The volume of intravenous contrast injection, and the rapid rate of injection, correlates directly with the degree of peak pancreatic gland enhancement. One study observed that an injection rate of 4 ml/sec of 150 ml of Omnipaque 300 provided peak pancreatic enhancement at 35–45-second scan delay at 122 HU [12]. Another study [13] observed time attenuation curves of an injection rate of 2.5 ml/sec compared with 5 ml/sec injection rate with 150 ml of contrast, which provided the pancreas a peak attenuation level of 65 HU at 69 seconds and a peak attenuation level of 84 HU at 43 seconds, respectively. A study [14] evaluated the effect of different injection rates and doses upon pancreatic gland enhancement. At 3 ml/sec injection, the average onset of pancreatic phase was 34–36 seconds, and at 5 ml/sec, the average onset of pancreatic phase occurred earlier at 26–28 seconds. Thus, there was earlier and more intense pancreatic gland enhancement with higher injection rates. The duration of pancreatic enhancement depended on the dose of contrast administered.

In a study performed by McNulty et al. in 2001, his team compared the mean attenuation values of the pancreatic adenocarcinoma, relative to the attenuation of the pancreatic parenchyma and peripancreatic parenchyma [12]. Tumor conspicuity was graded based upon the tumor-to-parenchymal attenuation, where the greatest

mean differentiation was demonstrated during the pancreatic parenchymal phase of enhancement of 49 Hounsfield units (HU) difference. No statistical difference was seen in the enhancement between the pancreatic parenchymal phase and portal venous phase. Maximal celiac and superior mesenteric arterial enhancement was seen during the pancreatic parenchymal phase delay. The maximal portal vein and superior mesenteric vein enhancement was observed during the portal venous phase. There was no advantage of adding the arterial phase imaging to the CT imaging protocol; thus, the early arterial phase is no longer recommended. A study reported pancreatic adenocarcinoma detection sensitivities for the different phases of imaging in tumor detection: pancreatic parenchymal phase (97%), portal venous phase (93%), and arterial phase (63%). A retrospective study reviewed patients that underwent surgery for pancreatic adenocarcinoma, with triphasic CT multi-detector CT evaluation [14]. The arterial phase was initiated at 30 seconds, pancreatic parenchymal phase at 40 seconds, and portal venous phase at 70 seconds after contrast injection. The mean sensitivities for the detection of pancreatic adenocarcinoma were 80.6% for the arterial phase images, 89% for the pancreatic parenchymal phase images, and 89% for the portal venous phase images. By using all phases of contrast enhancement and visualization of multiplanar reformations, the sensitivity for pancreatic adenocarcinoma was raised to 90%. The pancreatic parenchymal phase timing was better for the evaluation for arterial invasion or lymph node involvement. The portal venous phase of imaging was better for serosal and retroperitoneal extension and the assessment of portal vein invasion. The pancreatic parenchymal phase and portal venous phase of enhancement were equal in the evaluation of choledochal and duodenal invasion. Both the pancreatic phase and portal venous phase imaging demonstrated higher kappa value correlation than arterial phase imaging. Other studies used a fixed duration injection of 30 seconds and weight-based (2 ml/kg Omnipaque 300) concentration of intravenous contrast and determined that the mean contrast enhancement of the pancreas increased from 25 to 40 seconds and peaked at 35–45 seconds (82–85 HU) [15]. The mean peripancreatic arterial enhancement peaked at 25–40 seconds and the mean peripancreatic venous enhancement peaked at 55–60 seconds.

Given the individual variations in cardiovascular function and circulation times, others have evaluated the use of bolus tracking techniques to optimize the optimal scanning delay for MDCT for pancreatic imaging [16]. By placing an ROI (region of interest) within the abdominal aorta at the level of the diaphragm, injecting 2 ml/kg Omnipaque 300 at 4 ml/sec, a 50 HU trigger yielded an optimal mean peak contrast enhancement of the pancreatic parenchyma at a 15–20-second delay (84–85 HU). The peak main portal vein enhancement occurred at 25–30-second delay after trigger of the bolus tracking and the peak liver enhancement occurred at 45–55-second delay. However, the aortic transit time varied immensely between 7 and 33 seconds, with a mean aortic transit time of 15 seconds, secondary to marked differences in patient cardiac output and circulation times. If a fixed time delay were chosen, the pancreatic parenchymal phase would range from 30- to 35-second delay from the start of the contrast bolus injection and the hepatic parenchymal phase 60–70-second delay.

A multi-phase CT should be performed for the initial CT staging and pre-surgical workup, particularly to evaluate the primary tumor and to assess for vascular invasion. For follow-up imaging to monitor disease response, a dual-phase or single portal venous phase imaging may be considered. A pre-contrast CT is an optional phase and may be performed to evaluate for underlying glandular calcifications, ductal stones, or hemorrhage. If there is suspicion of a neuroendocrine tumor, the addition of an early pancreatic vascular phase at 20–25 seconds may be considered in addition to the pancreatic arterial parenchymal phase, but not routinely performed, to limit radiation dose.

A neutral oral contrast, usually water, is administered to distend the duodenal sweep and stomach during CT imaging. High-density oral contrast should be avoided, as the air/positive oral contrast interface can lead to beam hardening artifact, which may compromise imaging quality and may obscure vascular structures during 3D post-processing. In addition, effervescent granules can be used to distend the stomach, although the air-contrast level can produce a streak artifact. Glucagon has been given to the patient in the past to diminish peristalsis, but given the fast scan acquisitions of the new scanners, it is not needed.

For the imaging of pancreatic cancer, patients should undergo multiphasic CT imaging to optimize the visualization of the pancreas and other abdominal organs. As noted above, there is variability in the application of the bolus timing techniques. At our institution, we perform the following CT scan technique. 500 ml water is administered 15 minutes prior to the study to distend the stomach prior to imaging. A 20 gauge angiocath is placed in the antecubital fossa. We administer 1.8 ml/kg Omnipaque 350 IV at 3–5 ml/sec. We perform a baseline pre-contrast CT of the pancreas, limited to the pancreas, approximately the T12 to L3 levels on the AP scout. The purpose of the pre-contrast scan is to assess for calcifications, hemorrhage, and proteinaceous cysts and to determine if there is any enhancement of the pancreatic tumor elements. Centers that utilize a dual-energy or spectral CT scanner may forego the non-contrast phase, as a virtual non-contrast image may be processed from the dual-energy/spectral CT data set. Pancreatic parenchymal phase imaging is acquired at a fixed 40-second delay from IV contrast initiation and portal venous phase imaging at a 70-second delay. Scans are performed at 120 kVp, automatic mA tube modulation, on a GE 64 slice CT, 0.625 mm, from the top of the diaphragm to the top of the iliac crest for the pancreatic phase and from the top of the diaphragm to the pubic symphysis for the portal venous phase. Images are reconstructed at 2.5 mm thick slices and sent to the PACS picture archiving and communication system. Coronal and sagittal reformations are sent to PACS. 0.625 mm images are sent to our 3D independent workstation for image manipulation. We do not find any significant advantages to the delayed equilibrium phases to the evaluation of pancreatic cancer imaging, which increases the radiation dose to the patient (Table 1.1).

We reconstruct multi-planar reformation (MPR) images and 3D volume-rendered (VR) images for both arterial and portal venous phase images, to accurately assess the degree of vascular involvement of the celiac axis and superior mesenteric artery by tumor. Some institutions will routinely perform curved or oblique reformatted images to assess the peripancreatic vasculature and peri-neural structures, but curved reformations are not part of our routine practice.