# Imaging Recommendations for Diagnosis, Staging, and Management of Pancreatic Cancer

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## Abstract

Pancreatic cancer is the fourth most prevalent cause of cancer-related death worldwide, with a fatality rate equal to its incidence rate. Pancreatic cancer is a rare malignancy with a global incidence and death ranking of 14th and 7th, respectively. Pancreatic cancer cases are divided into three categories without metastatic disease: resectable, borderline resectable, or locally advanced disease. The category is determined by the tumor's location in the pancreas and whether it is abutting or encasing the adjacent arteries and/or vein/s.

The stage of disease and the location of the primary tumor determine the clinical presentation: the pancreatic head, neck, or uncinate process, the body or tail, or multifocal disease. Imaging plays a crucial role in the diagnosis and follow-up of pancreatic cancers. Various imaging modalities available for pancreatic imaging are ultrasonography (USG), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and 18-fluoro-deoxy glucose positron emission tomography (FDG PET).

Even though surgical resection is possible in both resectable and borderline resectable non-metastatic cases, neoadjuvant chemotherapy with or without radiotherapy has become the standard practice for borderline resectable cases as it gives a high yield of R0 resection.

**Keywords**

- ablation
- biopsy
- IRE
- magnetic resonance imaging
- multi-detector computed tomography
- oncology
- pancreatic neoplasms
- PET-CT

## Introduction

Pancreatic cancer is the fourth most prevalent cause of cancer-related deathworldwide,[1] with a fatality rate equal to its incidence rate.[2,3] While other cancers such as colorectal cancer, breast cancer, and prostate cancer have made significant advances in early detection and treatment, the prognosis for pancreatic cancer remains bleak. As per the latest American Cancer Society Cancer Facts & Figures Report, the 5-year survival rate is 11% across all stages and a mortality rate that has not decreased over the last few decades.[4,5] As a result, pancreatic cancer appears to be one of the most challenging cancers to combat.[6] In this article, we review the imaging findings relevant to diagnosis and surgical staging of pancreatic carcinoma. Apart of diagnosis, emphasis has been given to image guided management of pancreatic carcinoma.

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## Risk Factors and Etiopathogenesis

The risk factor can be inherited and non-inherited. Inherited include hereditary pancreatitis, cystic fibrosis, Peutz–Jeghers syndrome, hereditary nonpolyposis colorectal cancer with *MLH1* mutation, familial atypical multiple mole melanoma syndromes, hereditary breast and ovarian cancer 23.1% in *BRCA1* carriers and 6% in *BRCA2* carriers,[7] and familial pancreatic cancer. Noninherited risk factors include smoking, diabetes mellitus, chronic pancreatitis, obesity, physical activity, and cystic lesions.[7] During the development and spread of pancreatic cancer, multiple groups of genes undergo genomic alterations, i.e., either activation or inactivation. Oncogene activation and tumor suppressor gene inactivation are involved in the beginning and progression of pancreatic malignancies. Furthermore, dysregulation of molecules in various cell signaling pathways, such as EGFR, Akt, NF-B, and others, and their molecular interaction, play essential roles in pancreatic cancer molecular pathogenesis.[8]

## Epidemiology

Pancreatic cancer is a rare malignancy with a global incidence and death ranking of 14th and 7th, respectively. In India, pancreas ranks 24th with 10,860 new cases (1.03%) and 18th in mortality (9). The incidence is higher in the older population (more than 50% in those aged 65–75 years).[3] The incidence is the highest among Northeastern Indian regions. In India, pancreatic carcinoma is ranked 21st in males and 17th in females. Mizoram has the highest AAR (age-adjusted incidence rates), followed by Mumbai, Thiruvananthapuram, and Delhi in males and Mumbai, Delhi, Bengaluru, and Thiruvananthapuram in females.[9] In Indian registries, there is an inconsistent pattern due to the absence of reporting of all cases in registries.[9]

## Staging

The TNM staging system is used by the American Joint Committee on Cancer to assess immediate and long-term clinical prognosis and to create survival data for patients based on their illness stage. The T stage is determined by the tumor's size and its relationship (abuts/encases the vessels) with the vessels when there is an extra-pancreatic disease. The lack or presence of metastasis to regional lymph nodes or other distant sites determines the regional lymph node (N) and distant metastasis (M) stages.[10] The N categories only comprise regional lymph nodes found along lymphatic drainage channels that would be included in the surgical field and would be removed along with the underlying tumor. M1 stage lymph nodes are those that have spread outside of the usual drainage channels or are not routinely included in surgical resection.[11] The NCCN consensus report guidelines describe a tumor staging system and therapy recommendations based on the amount of the tumor. The NCCN uses the American Hepato-Pancreatico-Biliary Association (AHPBA) consensus report to determine resectability status. Pancreatic cancer cases are divided into three categories without metastatic disease: resectable, borderline resectable, or locally advanced disease.[12] The category is determined by the tumor's location in the pancreas and whether it is abutting or encasing the adjacent arteries and/or vein/s. The recommendations define "abutment" as less than or equal to 180° tumor contact of the vessel circumference and "encasement" as more significant than 180° tumor contact of the vessel circumference.[12,13] The term borderline resectable had extensive debate in the literature, hence many consensus such as AHPBA, MD Anderson and others had defined it and are listed in ►**Table 1**.[14–16] A few authors tried subclassifying borderline resectable (BR) further into BR-resectable and BR-locally advanced. NCCN had defined all BR-cases were vascular reconstruction is possible as borderline resectable and the rest as unresectable-locally advanced, provided no distant metastases.[17,18]

## Clinical and Diagnostic Workup

Because the pancreas is positioned in the retroperitoneum, where cancer grows slowly at first, symptoms are typically a sign of advanced disease. The stage of disease and the location of the primary tumor determine the clinical presentation: the pancreatic head, neck, or uncinate process, the body or tail, or multifocal disease.[19] Because most tumors in the pancreatic head occur in the right–upper quadrant or epigastric region, signs and symptoms may include right–upper quadrant or epigastric pain, jaundice, nausea, or vomiting due to obstruction of the gastric outlet, diarrhea,

**Table 1** Borderline resectability definitions-Comparison between different consensus

| Vessel involved | AHPBA/SSAT/SSO/NCCN | MD Anderson | Alliance (TVI) |
|---|---|---|---|
| Superior mesenteric vein/portal vein | Abutment/impingement/ encasement/short segment occlusion | Occlusion | TVI $\geq$ 180° of vessel wall circumference and or reconstructable occlusion |
| Superior mesenteric artery | Abutment | Abutment | TVI $<$ 180° of vessel wall circumference |
| Hepatic artery | Abutment/short segment encasement | Abutment/short segment encasement | Reconstructable short segment interface of any degree between tumor and vessel wall |
| Celiac artery | Uninvolved | Abutment | TVI $<$ 180° of vessel wall circumference |

AHPBA/SSAT/SSO/NCCN, Americas hepatopancreaticobiliary Associations/Society for the Surgery of the Alimentary Tract/Society of Surgical Oncology/National Comprehensive Cancer Network; TVI, tumor vessel interface.

and steatorrhea from pancreatic insufficiency. Although not always linked to malignancy, new development or worsening of previously stable diabetes should alert the clinician to the risk of pancreatic cancer.[20] In pancreatic cancer, tumor markers are of little diagnostic value. CA 19-9 (sensitivity 70%–90%, specificity 68–91%), which has a weak positive predictive value in both asymptomatic (0.9%) and symptomatic (72%) individuals, and carcinoembryonic antigen (sensitivity 25%–54%), similarly has a low diagnostic yield (specificity 75–91%), have also been studied.[21]

## Imaging Guidelines

Imaging plays a crucial role in the diagnosis and follow-up of pancreatic cancers. Various imaging modalities available for pancreatic imaging are ultrasonography (USG), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and $^{18}$ fluoro-deoxy glucose positron emission tomography (FDG PET). Imaging-guided interventions such as biopsy and fine needle aspiration cytology (FNAC) are essential for tissue diagnosis in this era of molecular and targeted therapies. Key imaging features and preferred modalities in various clinical settings are summarized in ►**Supplementary Tables S1** and **S2**, available online only. We will further discuss these modalities and their relevance in the following sections.

### Screening

No studies have defined the role of imaging-based screening in pancreatic cancers. However, a few upcoming studies suggest that imaging-based screening can be beneficial in candidates at risk of pancreatic cancers due to hereditary causes such as *BRCA* mutations, Li Fraumeni, Lynch, and Peutz–Jegher syndromes. Strong familial history and chronic pancreatitis are other target groups that might benefit from imaging screening, as both groups have a high risk of malignancy.[22] USG is a cost-effective screening modality and is widely available. However, dual-phase CECT and MRI can also be employed in high-risk candidates.[23,24] Many studies have shown that while MRI can detect small cystic lesions, EUS may be better able to detect small solid lesions when screening high-risk individuals for pancreatic cancer. In the Canto et al. research of 216 high-risk individuals, pancreatic abnormalities (cysts, solid lesions, or chronic pancreatitis) were seen in 42.6%, 33.3%, and 11% of patients, respectively, on EUS, MRI, and CT scan. In comparison to a sensitivity of 53% for a CT scan and a sensitivity of 67% for an MRI, this corresponds to an EUS sensitivity of 93% for the detection of solid lesions less than 2 cm.[25]

### Diagnosis

Both imaging and intervention play a role in the diagnosis of pancreatic cancer. The current modality of choice for diagnosis is dual-phase CECT, as preferred by the NCCN guidelines due to its superior contrast and spatial resolution. Other modalities such as USG, MRI, and PET-CT can also be employed for diagnosis in appropriate settings. Each modality's role, advantage, and drawback have been briefly explained below.

Ultrasonography: USG can be an effective and inexpensive modality for detecting a pancreatic mass. Shortcomings of USG include obese body habitus and bowel gas shadow. The overall reported accuracy of USG in pancreatic cancer detection is around 50 to 70%.[26] In the hands of an experienced radiologist, USG can be an effective initial diagnostic modality and can perform guided biopsies and FNAC. Hypoechoic hypovascular mass is the typical USG finding.[27]

Computed tomography: The NCCN criteria prefer dual-phase CECT over the conventionally performed single-phase CECT. Dual-phase CECT is now widely performed for the diagnosis of pancreatic cancer. It includes a contrast-enhanced CT scan using intravenous contrast injection at flow rates between 3 and 5 mL/s and acquiring pancreatic parenchymal phase at 35 to 40 seconds delay and the portovenous phase at 60 to 70 second delay.[27] The protocol for CT in pancreatic cancer imaging is provided in ►**Supplementary Table S3**, available online only. Optimal pancreatic parenchymal enhancement occurs in the pancreatic parenchymal phase giving better parenchymal to tumor attenuation difference as the latter is predominantly hypoenhancing. Also, the arterial anatomy and its relation to the tumor are best depicted in this phase.[28,29] The portovenous phase gives better portovenous opacification and helps identify their relationship with the tumor. Hepatic and nodal metastases can also be better studied in this phase. ►**Figure 1** depicts a radiologically resectable pancreatic cancer. CECT has a sensitivity of 76 to 92% in detecting pancreatic cancer. The major drawback of CECT is identifying isoattenuating pancreatic lesions, especially ones smaller than 2 cm.

Magnetic resonance imaging: The main indication for MRI is when an isoattenuating lesion is when no obvious lesion is appreciated on CECT in a case of suspected pancreatic cancer. Pancreatic adenocarcinoma is a hypovascular tumor rich in fibrous stroma. It appears hypointense on T1 and T2 and shows diffusion restriction, hypointense in the venous phase, and isointense in the delayed phase due to wash-in of contrast. Magnetic resonance cholangiopancreatography (MRCP) is the modality of choice to evaluate the ductal system. It is superior to CT and ERCP as it effectively demonstrates ducts both proximal and distal to the stricture.[30] The MRI protocol for pancreatic cancer imaging is provided in ►**Supplementary Table S4**, available online only. The major drawback with MRI is cost, time, and availability compared with CT. Compared to computed tomography, MRI is a non-ionizing cross-sectional imaging technique with a safer intravenous contrast profile (CT). This is crucial, especially for patients who need to have repeated imaging follow-up and are at a higher risk of radiation harm (such as younger patients). Less than 1 cm non-contour-deforming focal ductal adenocarcinomas that typically present as non-contour-deforming pancreatic lesions on CT can be well characterized using MRI.[31] With a sensitivity and specificity of 93% and 75%, respectively, the MR method using fat-suppressed T1-weighted 3D-GRE sequence is able to distinguish ductal adenocarcinoma from chronic pancreatitis.[32]

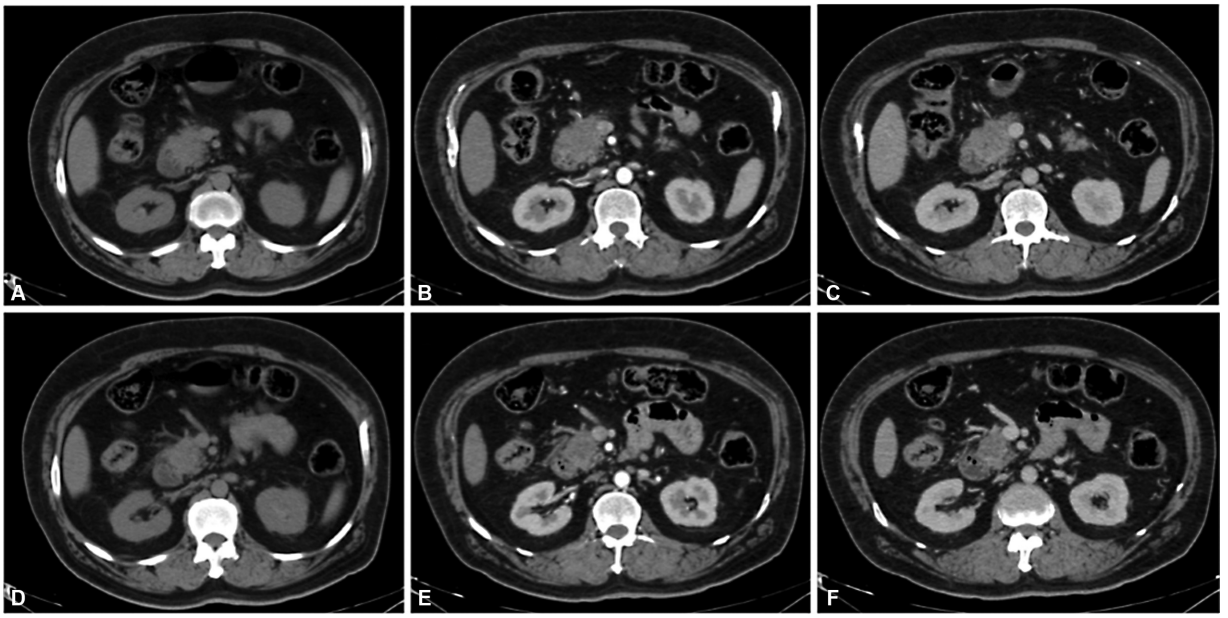


**Fig. 1** Axial CT images **A, D**-plain, **B, E**-pancreatic parenchymal, and **C, F**-portovenous phase depicts a hypodense hypoenhancing mass involving the head of the pancreas. Radiologically, this represents a resectable pancreatic carcinoma.

Fluoro-deoxyglucose positron emission tomography: Integrated FDG PET-CT has incremental value in detecting subtle lesions in CT-negative or equivocal cases. A study by Heinrich et al showed the sensitivity and specificity of PET-CT versus CT alone were 89% versus 93% and 69% versus 21%, respectively.[33] NCCN criteria suggest that PET-CT cannot be substituted for the conventional dual-phase high-resolution CECT. But PET-CT has added advantage in the detection of distant metastases and staging of pancreatic cancer.[34] Neurotensin receptors are overexpressed in pancreatic cancer cells and can be specifically targeted using radiolabeled neurotensin analogs. In a study of six patients with metastatic pancreatic adenocarcinoma using a neurotensin receptor antagonist coupled to 177Lu (177Lu-3BP-227) demonstrated feasibility, improvement of symptoms, and quality of life in all patients.[35]

In the current era, tissue diagnosis, including immunohistochemistry and molecular markers, is essential before any chemotherapy. EUS-FNA is still the gold standard for sampling pancreatic masses because of its high diagnostic accuracy, especially when combined with rapid on-site evaluation (ROSE) and low-risk profile. However, FNA has some inherent flaws, which include a limited volume of tissue with poor cellularity and the difficulty of ensuring a core tissue with intact histological architecture, making immunohistochemistry and molecular profiling difficult.[36] Pancreatic tissue sampling can be performed under USG and CT guidance. The preferred modality for immunohistochemistry is the biopsy, as it requires more tissue samples than conventional FNAC. USG-guided sampling is preferred in large masses, mass involving the head of the pancreas when there is no intervening bowel shadow. CT-guided sampling is the preferred modality in many cases as the pancreas is a retroperitoneal structure and in smaller lesions or lesions involving the body and tail of the pancreas where an adequate acoustic window is not possible. In cases where good access is not available, either a transgastric approach or hydrodissection with saline can be performed to create a window. Presently, all biopsies are performed with an 18-gauge semiautomatic biopsy needle, and for FNAC 22-gauge needle is used. Post biopsy dual-phase contrast CT has to be performed routinely for all patients to rule out any possible complications.[37,38] The approach for CT-guided pancreatic biopsy is depicted in ►**Supplementary Fig. S1**, available online only. FDG PET-CT has an advantage in guiding the biopsy to the most avid part of the tumor, thereby increasing the diagnostic yield.

## Staging

Dual-phase CECT is the modality of choice for the staging of pancreatic cancers and is done according to mostly followed TNM classification by AJCC or the resectability criteria proposed by the NCCN guidelines. Staging involves defining the tumor's location, extent, vascular involvement, nodal spread, and distant metastatic evaluation. The arterial and venous encasement is shown in ►**Supplementary Fig. S2**, available online only. Distant metastasis most commonly involves the liver, lungs, and peritoneum.[39] Hence, CT chest is usually acquired as a part of the venous phase of the dual-phase CECT. It is crucial to look for nodal spread and the number and location of the nodes, peritoneal disease, as these factors can affect the surgical resection. Alternative to CECT, MRI and FDG PET-CT can also be used for staging pancreatic cancer. FDG PET-CT effectively detects subtle nodal, peritoneal, and lung metastases, while MRI is better for local disease extent and liver, peritoneal and nodal metastatic evaluation.[40]

## Management

Even though surgical resection is possible in both resectable and borderline resectable non-metastatic cases, neoadjuvant

chemotherapy with or without radiotherapy has become the standard practice for borderline resectable cases as it gives a high yield of R0 resection. Dual-phase CECT is the imaging modality of choice for response assessment in both neoadjuvant settings and in the immediate postoperative period. Post chemotherapy response assessment scan shown in ►**Supplementary Fig. S3**, available online only shows a decrease in the tumor size. In immediate post-surgery settings, dual-phase CECT is necessary to rule out complications such as pancreatitis, gastroduodenal artery (GDA) stump pseudoaneurysm or bleeding, abdominal collections, and anastomotic leaks.[41,42]

Imaging in the neoadjuvant and adjuvant setting is challenging as the radiological response lags behind the histological response due to persistent soft tissue around the vessels as the tumor is mainly composed of fibrous stroma even if there is no viable tumor on histology. A recent study by Lee et al concluded that a reduction in metabolic tumor parameters of FDG-PET/CT after neoadjuvant chemotherapy indicates an improved overall survival and recurrence-free survival.[43] Other challenges are local edema and inflammatory reaction induced by radiation therapy. These factors necessitate careful reading of images to avoid overcalling the resectability status. The role of imaging in a palliative setting is to assess the response to therapy and detect the presence of new lesions or metastases.[44,45]

### Follow-up

NCCN recommends CECT as the modality of choice for post-treatment surveillance with a 3 to 6 monthly CECT for up to 2 years and yearly later. The average 5-year survival post curative therapy in pancreatic cancer is 20%.[45] Studies have demonstrated that routine imaging follow-up has survival benefits compared to performing imaging in symptomatic patients.

## Principles of Management

The current management strategies are based on the resectability criteria. The non-metastatic pancreatic carcinomas are subdivided into resectable, borderline resectable, and non-resectable. The management of choice for resectable cancers is upfront surgical resection. However, only 20% of the newly diagnosed cases fulfill the resectability criteria.[46,47] For tumors involving the head, uncinate process, and neck of the pancreas, Whipple's pancreatoduodenectomy and pylorus-preserving pancreatoduodenectomy are performed. In contrast, distal pancreatectomy is commonly performed for pancreatic body and tail tumors.[48,49]

For borderline resectable cases, the standard practice is to downstage the tumor with neoadjuvant chemotherapy with or without radiation, increasing the likelihood of future R0 resection. The widely used first-line chemotherapy regimen is FOLFIRINOX. The average 5-year survival percentage for pancreatic carcinoma for stages I–IV is 14%, 7%, 3%, and 1%.[50,51] Moreover, most patients will develop disease recurrence after curative-intent surgery, resulting in a 5-year survival rate of only 12 to 27% and median overall survival (OS) of 16.8 months. Newer advances in radiotherapy such as stereotactic body radiotherapy (SBRT) and intensity-modulated radiotherapy (IMRT) are widely used in borderline resectable cases to improve R0 resection rates.[43] Recently, irreversible electroporation (IRE), a nonthermal ablation technique, has been used in borderline resectable cases to improve survival.[52,53] Treatment options include chemotherapy, radiotherapy, and palliative bypass surgeries in unresectable and metastatic cases. Chemotherapy with or without radiation therapy is recommended for patients with unresectable disease, followed by attempted resection if the tumor is downstaged. FOLFIRINOX and gemcitabine-based regimes are the first lines of chemotherapeutic agents, with gemcitabine having lower efficacy but with a more tolerable side effects profile compared to FOLFIRINOX. Patients who have a response or stable disease after 4 months of chemotherapy may undergo maintenance therapy. For supportive care, ERCP or PTBD can be done for biliary obstruction or celiac plexus neurolysis for pain palliation is helpful.[54,55]

## Follow-Up Imaging and Management of Recurrent Disease

As per the NCCN guidelines, clinical evaluation and history for symptoms every 3 to 6 months for 2 years, then every 6 to 12 months as clinically indicated. CA 19-9 and follow-up contrast CT every 3 to 6 months is also recommended. Careful evaluation for postoperative bed soft tissue, peritoneal disease, and lung and liver metastases is essential.[56]

In a considerable percentage of patients, a multimodality approach to pancreatic cancer recurrence appears to provide effective palliation. In a small number of patients, radical excision of tumor recurrence may be possible. When compared to patients who receive chemoradiotherapy or supportive treatment, this subgroup of patients has a better chance of surviving longer. Furthermore, combining traditional therapies (e.g., chemoradiotherapy, surgery) with novel therapeutic modalities (e.g., RFA, IRE, stereotactic radiotherapy) may provide a new perspective on an otherwise fatal disease. To optimize the management of recurring tumors, accurate follow-up is required.[57,58]

## Summary

Imaging is crucial for pancreatic cancer surveillance, diagnosis, resectability assessment, and response assessment. To prevent unnecessary surgery, it is crucial for the radiologist to be aware of PDAC mimics. Structured reporting for complete and accurate assessment of the primary tumor, its relationship to/involvement of neighboring structures is an effective method for reporting pancreatic cancer and that it enhances assessment and surgeons' confidence. Future pancreatic cancer care will likely see a significant increase in the utilization of novel imaging tools and therapies, such as dual-energy CT, functional MR imaging techniques, and image guided techniques such as PTBD/SEMS, celiac plexus neurolysis, and IRE.

Conflicting Interest
None declared.

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