

Imaging of pancreatic cancer: An overview

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ABSTRACT

Pancreatic cancer (PaCa) is the fourth leading cause of cancer-related death in the United States. The median size of pancreatic adenocarcinoma at the time of diagnosis is about 31 mm and has not changed significantly in last three decades despite major advances in imaging technology that can help diagnose increasingly smaller tumors. This is largely because patients are asymptomatic till late in course of pancreatic cancer or have nonspecific symptoms. Increased awareness of pancreatic cancer amongst the clinicians and knowledge of the available imaging modalities and their optimal use in evaluation of patients suspected to have pancreatic cancer can potentially help in diagnosing more early stage tumors. Another major challenge in the management of patients with pancreatic cancer involves reliable determination of resectability. Only about 10% of pancreatic adenocarcinomas are resectable at the time of diagnosis and would potentially benefit from a R0 surgical resection. The final determination of resectability cannot be made until late during surgical resection. Failure to identify unresectable tumor pre-operatively can result in considerable morbidity and mortality due to an unnecessary surgery. In this review, we review the relative advantages and shortcomings of imaging modalities available for evaluation of patients with suspected pancreatic cancer and for preoperative determination of resectability.

KEY WORDS

pancreatic cancer; ultrasound; computed tomography; magnetic resonance imaging; endoscopic ultrasound guided fine needle aspiration

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Introduction

Pancreatic cancer (PaCa) is the fourth leading cause of cancer-related death in the United States. In 2010, there were over 43,000 estimated new cases of PaCa and over 36,000 deaths attributed to it in the United States (1). The estimated lifetime risk of developing PaCa is about 1 in 71 (1.41%) (2). The disease is rare before age 45 but incidence rises rapidly after that and peaks in the seventh decade of life. The major risk factors include smoking (3), hereditary predisposition to PaCa itself or to multiple cancers (4) and to a lesser degree, chronic pancreatitis (5). PaCa does not exhibit early symptoms and initial symptoms are often

nonspecific. Classical presentation of PaCa (painless jaundice) is present in only 13-18% of the patients and is often accompanied by pruritus, acholic stools dark urine, and weight loss (6). Abdominal pain is present in 80-85% of patients with locally advanced or advanced disease. Acute pancreatitis and new onset diabetes mellitus can often be the initial presentations of PaCa (7,8).

In up to 75% of the cases, the tumor is located within pancreatic head mostly sparing the uncinate process. Tumors in the pancreatic head often present early with biliary obstruction. However, tumors in the body and tail can remain asymptomatic till late in disease stage. Surgical resection is the standard of care for treatment but only but <10% of patients with pancreatic tumors have resectable tumors at the time of presentation. The criteria for unresectability include infiltration of superior mesenteric artery (SMA) and/or celiac artery or the presence of distant metastasis including metastatic celiac or mediastinal lymph nodes. The size of pancreatic tumor is a major determinant of resectability and up to 83% of tumors \leq 20 mm are resectable compared to only 7% of tumors $>$ 30 mm in size (9). The 5 year survival rate in patients with resectable tumors can be as high as 20-25% and compares favorably with patients with unresectable tumor, very few of whom survive 5 years after diagnosis. Imaging techniques

No potential conflict of interest.

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currently used for diagnosis and preoperative staging of pancreatic cancer include abdominal ultrasound (US), contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), MR cholangiopancreatography (MRCP) and invasive imaging modalities like endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS).

Imaging Modalities

Abdominal Ultrasound (US)

Abdominal ultrasound (US) is widely available, non-invasive, relatively inexpensive imaging modality without contrast associated adverse effects. It is usually performed to rule out choledocholithiasis and look for biliary dilation in patients who present with jaundice and abdominal pain. The real world accuracy of conventional US for diagnosing pancreatic tumors is 50 to 70% (10). The results of US are highly operator dependant. In addition, body habitus (adipose tissue), overlying bowel gas and patient discomfort can limit the use of US in evaluating the pancreas. If an initial US excludes choledocholithiasis in a patient with signs and symptoms to suggest a pancreatic etiology, CT or MRI is commonly used for further evaluation.

Computerized Tomography (CT)

Computerized tomography (CT) is the initial comprehensive imaging done in patients with suspected PaCa. Since the past decade, advances in CT technology have improved its accuracy in diagnosing and tumor staging of PaCa.

Non-contrast CT

Ideally, use of non-contrast CT to evaluate pancreas is limited to patients with renal failure or allergic reactions to iodinated contrast agent used. As the pancreatic tumors are hypovascular and can be visualized only with contrast imaging, non-contrast CT scans have poor sensitivity and specificity for pancreatic tumors and hence cannot be relied on to make a diagnosis.

CT with Intravenous (IV) contrast

Multidetector CT (MDCT) provides very thin slice cuts, higher image resolution and faster image acquisition. This technique allows better visualization of the pancreatic adenocarcinoma in relation to the SMA, celiac axis, superior mesenteric vein (SMV), and portal vein as greater parenchymal, arterial, and portal venous enhancement is achieved when imaging the pancreas with MDCT. This

can potentially aid in early detection and accurate staging of pancreatic carcinoma (11,12). MDCT with intravenous contrast is, therefore, generally considered as the imaging procedure of choice for initial evaluation of most patients suspected to have pancreatic cancer (13). It has reported sensitivity between 76%-92% for diagnosing pancreatic cancer (14-18). Pancreatic ductal adenocarcinoma is hypovascular and therefore enhances poorly compared to the surrounding pancreatic parenchyma in the early phase of dynamic CT and gradually enhances with delayed images. As a result, on contrast enhanced CT, pancreatic adenocarcinoma is typically seen as a hypoattenuating area but may occasionally be isoattenuating to the surrounding normal parenchyma thereby leading to misdiagnosis. Prokesch et al have reported that indirect signs such as mass effect on the pancreatic parenchyma, atrophic distal parenchyma, and abrupt cut off of the pancreatic duct PD dilation (interrupted duct sign) are important and should be considered as indicators of tumors when mass cannot be clearly identified on CT (19). Multiple studies have reported extrahepatic biliary dilation and/or PD dilation (double duct sign) as findings suggestive of PaCa (20). It is also important to be aware of changes to the parenchyma caused by chronic pancreatitis as they can closely mimic the changes due to PaCa and may lead to misdiagnosis. Contrast enhanced MDCT can be used to evaluate local extension, invasion of adjacent vascular structures and surgical resectability with an accuracy of 80 to 90% (21). However for pre-operative staging, it is limited in detecting liver metastases and early lymph node metastasis (22,23). The absolute contra-indications of contrast CT are in patients with renal failure and contrast allergy.

Pancreatic protocol CT (CT angiography)

Preoperative staging and assessment of resectability is usually performed using pancreatic protocol CT or CT angiography. CT angiography is done by bolus administration of iodinated nonionic contrast with imaging done in arterial and venous phases after intravenous injection of contrast. The arterial phase of enhancement, which corresponds to the first 30 seconds after the start of the contrast injection, provides excellent opacification of the celiac axis, superior mesenteric artery, and peripancreatic arteries. The portal venous phase, which is obtained at 60 to 70 seconds after the start of the contrast injection, provides better enhancement of the superior mesenteric vein, splenic and portal veins as well as the pancreas itself and any liver metastases that may be present. Even though pancreatic protocol CT is widely regarded to be superior to non-pancreatic protocol contrast MDCT for determining resectability, there is currently insufficient direct evidence

to support this.

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangiopancreatography (MRCP)

Magnetic resonance imaging (MRI) can be used in imaging for PaCa in patients with equivocal findings at ultrasound or MDCT. MRI examination of the pancreas is done with intravenous administration of contrast material and gadolinium is the most commonly used agent. PaCa is hypointense on gadolinium-enhanced T1-weighted images in the pancreatic and venous phases because it is hypovascular with abundant fibrous stroma compared to the pancreatic parenchyma. Tumors appear isointense on delayed images because of slow wash-in of contrast medium. MRI is commonly used to detect PaCa when a mass lesion is not identifiable on CT scan. There is however no significant diagnostic advantage of MRI over contrast-enhanced CT (sensitivity of 86% on CT vs. 84% on MRI) (24). Combining the two tests does not improve upon what is achieved with one test alone. MRI is better at characterizing cystic lesions of the pancreas and can provide some indirect radiological evidence to aid in diagnosis of pancreatic cancer. The choice of MRI or CT usually depends upon available local expertise and the clinician's comfort with one or the other radio-imaging technique. It is contraindicated in patients with metal in the body (e.g.: pacemakers, implants) and contrast allergy.

Magnetic resonance cholangiopancreatography (MRCP) is a useful adjunct to other radiographic diagnostic techniques and may emerge as the preoperative imaging procedure of choice for patients with suspected PaCa. MRCP uses magnetic resonance technology to create a three dimensional image of the pancreaticobiliary tree, liver parenchyma, and vascular structures. MRCP is better than CT for defining the anatomy of the biliary tree and pancreatic duct, has the capability to evaluate the bile ducts both above and below a stricture, and can also identify intrahepatic mass lesions. It is reportedly as sensitive as ERCP in detecting pancreatic cancers and unlike conventional ERCP, does not require contrast material to be administered into the ductal system (25). Thus, the morbidity associated with endoscopic procedures and contrast administration is avoided. Although MRCP has not yet completely replaced ERCP in patients with suspected pancreatic cancer in all centers, it is routinely used in patients with high grade stenosis of the gastric outlet or proximal duodenum or in those with certain post-surgical anatomy (e.g., Billroth II, Roux-en Y biliary bypass), which make the biliary ductal system difficult to access by ERCP (26). Chronic pancreatitis can be difficult to differentiate

from pancreatic adenocarcinoma on MRI since both show low signal intensity on T1-weighted images and both may be associated with pancreatic and/or biliary ductal obstruction. Dynamic gadolinium-enhanced MRI cannot differentiate chronic pancreatitis and PaCa on the basis of degree and time of enhancement (27). MRCP images may be more helpful in distinguishing between chronic pancreatitis and pancreatic adenocarcinoma especially if the duct-penetrating sign signifying a non-obstructed main pancreatic duct is present (28).

Positron Emission Tomography (PET) Imaging

Positron emission tomography (PET) scanning with the tracer 18-fluorodeoxyglucose (FDG) relies upon functional activity to differentiate metabolically active proliferative lesions such as cancers, most of which are FDG-avid lesion such as cancers from benign lesions, most of which do not accumulate FDG with the exception of inflammatory lesions such as chronic pancreatitis. The utility of PET in the diagnostic and staging evaluation of suspected PaCa remains uncertain and there is still no consensus on whether PET provides information beyond that obtained by contrast-enhanced CT (29). As PET imaging is usually performed after the initial CT, the sensitivity and specificity of PET varied depending on the CT result. Sensitivity and specificity after a positive CT was 92% (87 to 95) and 68% (51 to 81); after a negative CT, the corresponding values were 73% (50 to 88) and 86% (75 to 93). Elevated serum blood glucose levels increase the number of false negative PET scans. Data published on the use of PET scans in PaCa are conflicting. Some studies suggest that PET is useful for identifying metastatic disease that is missed by CT (30), while others reported that PET often misses small volume metastases within the peritoneum and elsewhere, including the liver (31).

More recent studies have investigated the value of integrated PET/CT, which has better spatial resolution as compared to PET scans. In one case series, the sensitivity and specificity of PET/CT for the diagnosis of PaCa compared with CT alone was 89% versus 93% and 69% versus 21% respectively (32). PET/CT is also superior to conventional imaging (MDCT, CT angiography, EUS) used for tumor staging and detection of distant metastases (sensitivity and specificity rates were 89 versus 56 and 100 versus 95 percent, respectively). A major limitation of this study was that the CT component of PET/CT was performed without the use of intravenous contrast material. When compared to MDCT with contrast, currently available data does not show that PET or integrated PET/CT provide any additional information. Further studies are

needed to evaluate the role of PET for diagnosis and staging especially in patients with a negative or indeterminate MDCT.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

Endoscopic Retrograde Cholangiopancreatography (ERCP) is used for diagnosis and palliation in patients with known or suspected pancreatobiliary malignancies. During an ERCP, cannula is passed from the endoscope into the pancreatic or biliary ducts. Contrast dye is injected through the cannula into the ducts and the biliary and pancreatic ductal systems are visualized fluoroscopically. In contrast to other imaging modalities, tissue diagnosis of the involved ducts may be achieved using needle aspiration, brush cytology, and forceps biopsy. Brush cytology has 35-70% sensitivity and 90% specificity (33). Triple sampling using brush cytology, FNA and forceps biopsy of biliary stricture during ERCP improves the sensitivity for diagnosing cancer to 77% (34). ERCP and brushing of biliary stricture has better diagnostic accuracy for cholangiocarcinoma (about 80%) compared to pancreatic carcinoma (35). ERCP has a limited role in staging of pancreatic and biliary cancers.

Palliation of biliary obstruction in patients with pancreatic and biliary cancer may be performed with biliary stent placement with ERCP or a surgical bypass. The available evidence does not indicate a major advantage to either alternative, so the choice may be made depending on clinical availability and patient or practitioner preference. ERCP is a widely available imaging modality and this modality may be preferable to surgery in some cases due to lower overall resource utilization and shorter hospitalization. The role of ERCP in biliary drainage prior to surgery for potentially resectable pancreatic cancers is currently debated and should be individualized based on specific clinical situation. However, the vast majority of patients with PaCa has an unresectable or borderline resectable tumor requiring chemotherapy \pm radiation and would benefit from an ERCP for biliary drainage. Acute Pancreatitis is a side effect encountered after ERCP in 5-7% of the patients. Gastrointestinal bleeding, perforation, infection and sore throat are other less common complications of ERCP.

Endoscopic Ultrasound Guided Fine Needle Aspiration (EUS/EUS-FNA)

EUS/EUS-FNA is used for definitive diagnosis of PaCa or in patients with suspected cancer not diagnosed by conventional imaging. EUS examinations are usually performed using radial echoendoscope initially and

whenever a suspicious 'mass' lesion is identified during the EUS exam, fine needle aspiration (FNA) is performed using a linear echoendoscope. Fine needle passes are made using a EUS-FNA needle in the same sitting. The cytology specimens are usually stained by the Diff-Quik and Papanicoulou method (Pap smear) and sample is collected for cell blocks. The final diagnosis is based on examination of the Pap smears and the cell blocks using standard cytologic criteria (36). Special cytology stains are used as indicated to diagnose neuroendocrine tumors. The sensitivity of EUS-FNA for diagnosing pancreatic cancer has ranged from 80-95% in various published studies (37-39). The performance characteristics of EUS-FNA for diagnosing PaCa seem to be influenced by presence of obstructive jaundice at initial clinical presentation and presence of underlying chronic pancreatitis. In patients without obstructive jaundice, the diagnostic accuracy of EUS-FNA is very high (98.3%) and is not significantly influenced by presence of underlying chronic pancreatitis. However, in patients presenting with obstructive jaundice, the sensitivity(92.0%) and accuracy(92.5%) of EUS-FNA for diagnosing malignancy is significantly lower especially so in patients with chronic pancreatitis (40). Absence of an identifiable mass lesion on EUS rules out PaCa with almost 100% certainty in the hands of experienced endosonographers (41). The accuracy of EUS-FNA for PaCa diagnosis can be further improved with use of adjunctive immunostaining in slides obtained by smearing EUS-FNA specimens (42). EUS is helpful in further evaluation of patients with non-specific and subtle findings suggestive of PaCa on CT and MRI imaging. We had earlier reported in non-jaundiced patients with "enlarged head of pancreas" or "dilated PD with or without a dilated CBD" on CT/MRI, a pancreatic malignancy was present in 9.0% of patients and EUS-FNA diagnosed cancer in these patients with 99.1% accuracy (43).

EUS probably has a role in preoperative staging of PaCa for determining resectability. Portal vein and splenic vein invasion are visualized better with EUS. However, tumor involvement of SMA and SMV is not reliably determined by EUS. In published studies, EUS has a T-stage accuracy of 78-94% and N-stage accuracy of 64-82% (44-49). However, the presence of biliary stent at the time of EUS examination reduced the T-stage accuracy to 72% (50). EUS also plays a role in identification and biopsy of metastatic peripancreatic, celiac and mediastinal lymph nodes for tumor involvement. Ahmed et al., questioned the role of EUS for T-staging and found its accuracy between 49% and 69% in two different studies (51,52). With recent advances in CT and MRI technology and the ability to perform image reconstruction, very detailed evaluation of vascular

infiltration by tumors is now possible. EUS imaging probably has an adjunctive role in T-staging of pancreatic tumors. However, due to its ability to reliably identify lymph nodal metastasis in celiac and mediastinal lymph nodes, EUS-FNA can prove to be beneficial in pre-operative assessment of resectability (53,54). The main limitation of EUS is its operator dependence and limited availability of expert endosonographers for accurate reporting. EUS carries a 0.1-1% risk of pancreatitis. As with any invasive procedure, complications like bleeding, tear, anesthetic complications can occur but are rare.

In conclusion, MDCT is the preferred initial imaging modality in patients with clinical suspicion for pancreatic cancer. The role of MRI for use in pancreatic cancer diagnosis is evolving and is currently used interchangeably with MDCT for this purpose. MRCP seems promising in differentiating pancreatic cancer from chronic pancreatitis. PET scans can provide information on occult metastasis but its clinical benefit is not established. EUS is the most accurate examination for diagnosing pancreatic cancer and can be a useful adjunct to CT/MRI in determining resectability of pancreatic cancer. EUS/EUS-FNA can also provide a definite determination about the presence of pancreatic cancer in patients with non-specific findings suggestive of cancer on conventional imaging.

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