9
Recent Advances in Imaging of Pancreatic Neoplasms

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Key Points

- The use of specific imaging modalities in the workup of pancreatic neoplasms is dependent on local expertise, and, thus, familiarity of the ordering physician with multiple imaging techniques is paramount.
- While clinical symptoms can be suggestive of pancreatic cancer, pancreatic lesions are often detected incidentally. Some of these can be definitively characterized by imaging.
- Common diagnostic problems in pancreatic imaging include differentiating post-operative changes versus recurrent disease, and adenocarcinoma versus chronic pancreatitis.
- Multi-detector CT is the mainstay of abdominal imaging, and many surgeons will operate based on CT findings of neoplasm alone. MRI and endoscopic ultrasound are utilized as problem-solving tools.
- Endoscopic ultrasound has the highest sensitivity and specificity for locoregional extension of tumors, however must be performed in conjunction with other cross-sectional imaging (e.g., MDCT) to exclude peritoneal disease.
- FDG-PET has average sensitivity and specificity for pancreatic adenocarcinoma, and ongoing research suggests that FLT-PET may be more tumor-specific than FDG-PET. This modality shows promise in assessment of therapeutic tumor response and disease recurrence.
- Although spatial resolution of some current imaging techniques can reach submillimeter level, novel imaging techniques will require the exploitation of cellular differences between normal and abnormal tissue in order to improve resolution.
- Morphologic changes occur later than cellular changes in cancer treatment, and newer perfusion imaging techniques (CT perfusion, DCE-MRI) attempt to

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quantify changes in tissue perfusion as tumoral angiogenesis is targeted by newer drugs.
- The multiple techniques available in pancreatic imaging should be viewed as complementary to answer the clinical question.

Oncologic imaging of the pancreas is a challenging entity due to a large number of primary pancreatic neoplasms, as well as benign entities of the pancreas that simulate neoplasms, such as inflammatory and cystic disease. While clinical and laboratory data are able to distinguish many of the disease processes affecting the pancreas, imaging is inevitably tied to diagnosis and treatment, given the significant overlap of patient symptoms in benign and malignant pancreatic disorders. In general primary pancreatic neoplasms can be divided into three categories: solid, cystic and neuroendocrine tumors. All three of these can overlap in common imaging findings, and familiarity with available imaging modalities can help differentiate these tumors from benign disease. This chapter will discuss current and emerging techniques in pancreatic imaging, as well as their integration with oncologic care.

1 Epidemiology

Pancreatic ductal adenocarcinoma is the fourth most common cause of death among malignancies, with 33,370 deaths projected in 2007. In this year 37,170 new cases are expected, and the small difference between these two values reflects the aggressiveness of this tumor and its poor prognosis [1]. Early detection of pancreatic malignancy is paramount, as five-year survival falls off sharply, from a low of 20 percent to less than 5 percent, as local disease progresses to regional or metastatic disease [1]. Surgical resection currently offers the only chance of cure.

Hereditary pancreatitis confers the highest cumulative risk at 30 percent to 40 percent, and chronic pancreatitis from multiple causes is also significantly contributory [2-4]. Specific pancreatic lesions, which include intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasms (MCNs), are also associated with the subsequent development of adenocarcinoma at the site of the lesion [5], or at sites remote from the primary detected lesion [6]. We are beginning to understand that precursor lesions to pancreatic adenocarcinoma exist. A new nomenclature system has been devised [7], incorporating the term pancreatic intraepithelial neoplasia (panIN), which are non-invasive cellular changes present in pancreatic ducts. PanINs contain mutations associated with invasive adenocarcinomas, and further study into the carcinogenesis and the simultaneous existence of adenocarcinoma and other precursor lesions is necessary [8] (Fig. 9.1).

While adenocarcinoma is the most lethal solid pancreatic neoplasm, a significant proportion of pancreatic lesions are of the cystic variety. Pancreatic cystic lesions are present in 15 percent to 24 percent of the population, based on recent studies

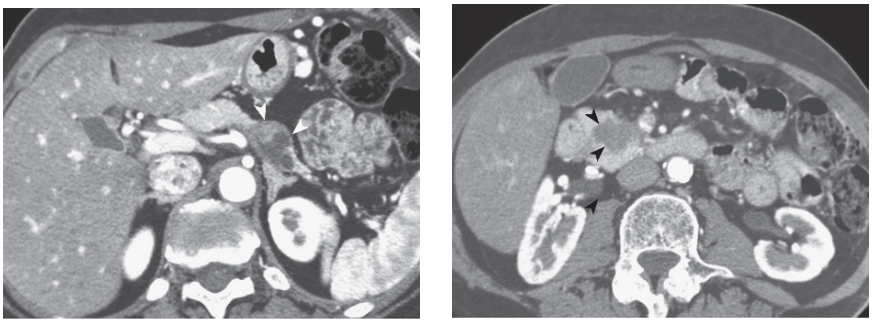


Fig. 9.1 Multifocal pancreatic neoplasia. **(a)** Axial contrast-enhanced MDCT image of the pancreas shows a mucinous cystic neoplasm with a focal mural nodule (arrowheads). This was treated by surgical resection. **(b)** Follow-up axial MDCT image shows absence of the pancreatic body and tail consistent with surgery. A new hypodense lesion in the pancreatic head (arrowheads) was biopsy-proven adenocarcinoma, remote from the original disease

[9, 10]. Cystic neoplasms include entities such as serous and mucinous tumors. Serous cystadenomas are a common lesion, consisting of up to 25 percent of all cystic pancreatic tumors. Mucinous tumors represent 2 percent to 5 percent of all exocrine neoplasms, and consist of mucinous cystadenoma, mucinous cystadenocarcinoma and intraductal papillary mucinous neoplasm (IPMN). IPMNs vary in incidence from 1 percent to 8 percent. The serous cystadenoma is a common benign neoplasm, while mucinous cystic neoplasms range from benign to malignant. These can, however, be borderline or low-grade malignancies which are associated with the development of adenocarcinoma, depending on the amount of cellular atypia present [11, 12]. Differentiating cystic pancreatic neoplasms from benign cystic-appearing lesions is a primary clinical and imaging concern, and can be challenging if the natural history of these lesions is not understood.

One area in which solid and cystic lesions can have imaging overlap is in the setting of neuroendocrine tumors. Neuroendocrine tumors are generally rare, and 85 percent of patients present with a clinical syndrome, depending on the type of tumor [13]. The majority of these tumors are small solid lesions. Cystic neuroendocrine tumors are even less common, but still comprise up to 4 percent of all pancreatic tumors [11]. The clinical presentation of these tumors overlaps with other clinical disorders, which is why imaging can be useful in confirming the presence of these lesions, especially when they are small.

1.1 Imaging Principles and Diagnostic Dilemmas

The goal of pancreatic imaging is the early detection and characterization of clinically relevant pancreatic lesions. Unfortunately, incidental cystic pancreatic lesions detected by multi-detector computed tomography (MDCT) are increasingly common

and can range from benign incidental lesions to malignant. The resection of all cystic lesions is impractical, as a significant proportion of these lesions are benign. Given the high prevalence of pancreatic cysts, current imaging recommendations are being developed to guide management decisions.

As the technology of existing imaging modalities improves, and new modalities are developed, it is important to recognize that all modalities have certain proven clinical uses, as well as limitations. Physicians must recognize and have an appreciation for the expertise that is available in their medical community to best integrate imaging findings with subsequent patient management.

Lesion detection and characterization are the primary goal of radiologists. Imagers attempt to divide the aforementioned pancreatic abnormalities into "malignant or benign," and "cystic or solid." Occasionally, it can be difficult to answer these questions, and we need to utilize multiple imaging modalities to troubleshoot.

2 Imaging Features

2.1 Solid and Neuroendocrine Tumors

Pancreatic adenocarcinoma is a dense fibrotic tumor with decreased vascularity, compared to the remainder of the gland and, thus, tumor to glandular contrast is an essential goal of imaging by whatever modality utilized for detection [14]. It is known that five-year survival in the setting of adenocarcinoma is significantly higher when lesions are detected < 1 cm [15]. Thus, this tumor is utilized as the reference lesion, which we need to exclude in cases of characterization and detection.

When focal solid pancreatic lesions are detected, diagnosis can be aided by clinical and laboratory history, especially in the case of functioning neuroendocrine tumors or with invasive tumors causing biliary or pancreatic ductal obstruction. Additionally, certain imaging features on CT and MRI can be useful in narrowing a differential diagnosis. Examples of helpful imaging features include a "hypervascular" lesion, which narrows the differential diagnosis to include neuroendocrine tumors; hypervascular metastases such as renal cell carcinoma, thyroid cancer and melanoma, as well as occasionally pseudopapillary tumors. "Hypovascular" masses include adenocarcinoma and lymphoma, although the latter is a rare lesion. Lesions which are large include pseudopapillary tumors and non-functioning islet cell tumors and, less commonly, adenocarcinoma as this lesion tends to present earlier, secondary to patient symptoms [16]. It is important to recognize that large solid tumors can necrose and appear cystic. Calcification is also useful, as this can occur in large lesions when they undergo necrosis, such as in non-functioning islet cell tumors and pseudopapillary lesions. MRI is able to detect hemorrhage which is commonly seen in pseudopapillary lesions, although patient demographics (young females) will also help identify this lesion [16, 17].

Included in focal pancreatic abnormalities is the increasingly recognized non-neoplastic entity of autoimmune pancreatitis. This consists of hypergammaglobulinemia,

mild/no clinical symptoms and occasional association with other autoimmune disorders [18]. Imaging features can include focal or diffuse pancreatic enlargement. In the presence of focal glandular enlargement, the features of vascular invasion seen in adenocarcinoma are characteristically absent. Common bile duct obstruction and pancreatic duct narrowing are common and, thus, imaging overlap with adenocarcinoma is important to recognize. While not a neoplasm, this condition is becoming increasingly diagnosed by imaging [19]. Additionally, as autoimmune pancreatitis is steroid-responsive, it is of critical importance for this differential diagnosis be included in the evaluation of focal pancreatic abnormalities.

2.2 Cystic Lesions

Cystic and ductal mucinous tumors also have radiologic and clinical features which can help weight the differential diagnosis. Microcystic and macrocystic patterns have been described corresponding to serous cystadenoma and mucinous cystadenomas. If a cystic lesion can be shown to connect to the pancreatic duct with MDCT, endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP), it is likely a variant of IPMN. With a history of pancreatitis, pancreatic pseudocyst can be suggested, especially if there are imaging findings of pancreatitis such as glandular calcifications seen in chronic pancreatitis. When complexity is noted within a lesion, such as mural nodularity or rim-like calcification, pre-malignant or malignant lesions should be suspected, as in cases of mucinous cystic neoplasms (mucinous cystadenocarcinoma or malignant IPMN) [12, 20] (Fig. 9.2). In the case of IPMN, other features predictive of malignancy include main duct dilatation, diffuse ductal/multifocal involvement and large lesion size for branch type lesions [21]. A recent study looking at cysts < 3 cm on CT and magnetic resonance imaging (MRI) has shown that unilocular cysts are usually benign (97 percent PPV), while septations are associated with low-grade malignancy in 20 percent of cases [22]. The presence of any visible solid component is associated with invasive carcinoma [23, 24]. In IPMN, malignancy is reported in 7 percent to 46 percent of cases, varying from carcinoma in situ to frank adenocarcinoma [21].

2.3 Surgical and Clinical Principles

When imaging and clinical features suggest malignancy, it is important to recognize findings that indicate tumoral unresectability from a surgical standpoint. While visualized contact of neoplasm with adjacent vasculature on cross-sectional imaging is predictive of invasion based on the amount of contact [32, 33], a more recent paper has suggested that arteries and veins may need different criteria for invasion by cross-sectional imaging, as arteries are likely more resistant to invasion based upon their inherently stronger and thicker muscular wall [34, 35].

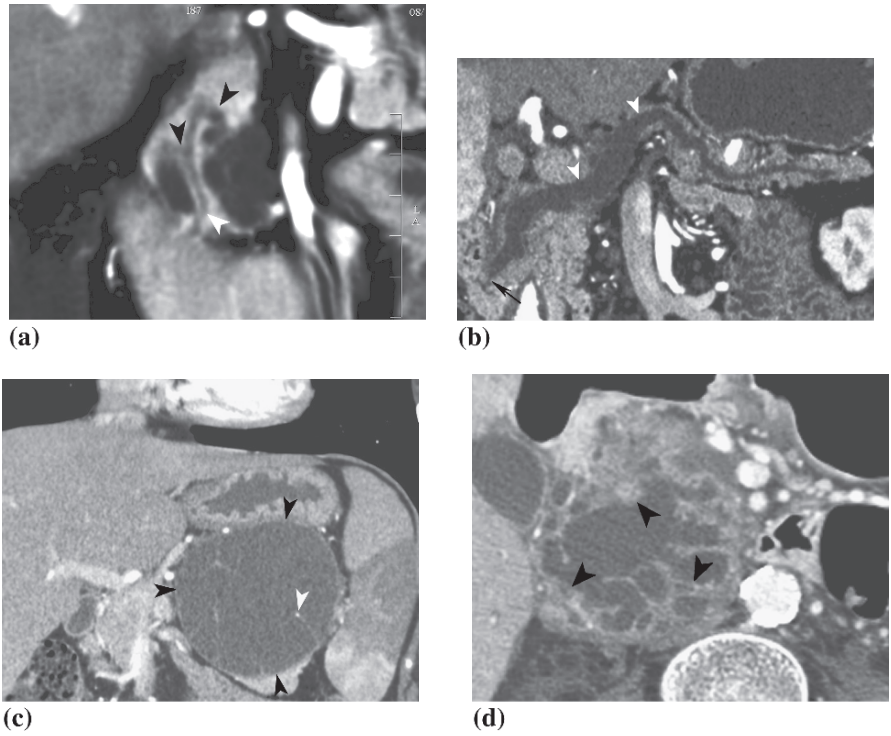


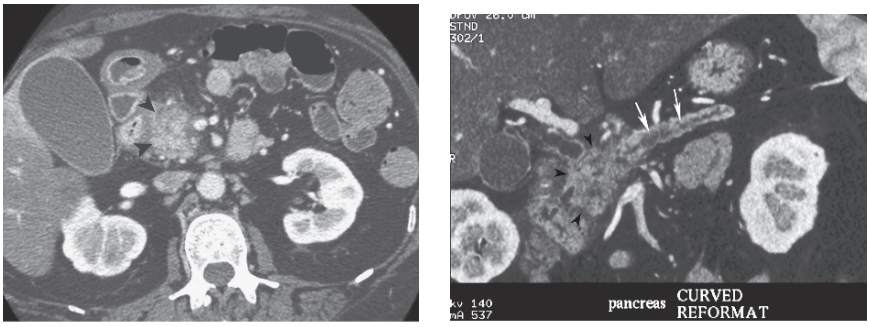
Fig. 9.2 Mucinous neoplasms. **(a)** Side-branch type IPMN. Note the pancreatic duct (white arrowhead) and connections of the mucinous low density lesions to the duct (black arrowheads). If this connection can be demonstrated, the diagnosis is solidified. **(b)** Main duct type IPMN. Note the dilated main pancreatic duct (white arrowheads), tapering at the ampulla (black arrow). This dilated and tapered duct pattern, with isolated pancreatic ductal enlargement, is consistent with this diagnosis. **(c)** Mucinous cystadenoma. A focal cystic pancreatic mass is noted in the pancreatic body (black arrowheads). Thin septae are seen internally, one with focal calcification (white arrowhead). Peripheral or septal calcification is fairly specific for mucinous lesions. **(d)** Malignant IPMN. A complex cystic pancreatic head mass shows thick septations, and mural nodularity (arrowheads). These features are associated with malignancy

Ductal involvement in pancreatic adenocarcinoma may not be easily detected by routine cross-sectional imaging unless macroscopic ductal changes are present, such as focal ductal dilatation. When ductal changes are evident, difficulty in differentiating changes of chronic pancreatitis from adenocarcinoma occurs when tumor markers are not elevated, and when other glandular findings of chronic pancreatitis are not present on cross-sectional imaging, such as diffuse calcifications. A change in ductal caliber can either be due to focal stricture or an underlying mass that is too small to detect. Even with endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA), diagnostic success is not perfect, often requiring multiple passes to exclude malignancy in the setting of a benign lesion [40, 41]. Direct comparison of EUS-guided pancreatic FNA with CT-guided pancreatic FNA suggest that EUS-guided FNA may have the highest sensitivity [42, 43], however other studies have shown

that diagnostic rates and sensitivity are similar for both EUS and CT [44]. Given that EUS has been shown to be the most sensitive imaging examination for small tumors, FNA at the time of the study may be more prudent. Additionally, the complication of peritoneal seeding has been raised using percutaneous methods of sampling [45].

The issue of pancreatitis (either chronic or focal acute) versus tumor is one of the most important issues in pancreatic imaging today. Up to 20 percent of patients with chronic pancreatitis can develop a focal mass which simulates tumors [28] (Fig. 9.3). While the presence of a non-obstructed pancreatic duct coursing through a focal pancreatic lesion has good accuracy for diagnosing a pseudotumor of chronic pancreatitis [46], this sign as described by MRCP is often equivocal in clinical practice, necessitating further study.

Other significant problems affecting radiologic imaging are in the detection of micrometastatic disease to liver and peritoneum, as well as in the underestimation of vascular invasion [35]. One approach to this problem is to have patients who are candidates for resection undergo laparoscopy prior to or at the time of surgery. This is a controversial topic with its proponents stating that its routine use prior to pancreatic tumor resection will increase sensitivity for peritoneal disease in 15 percent to 51 percent of patients. Currently, even with advanced imaging techniques, unresectable disease is found at surgery in 20 percent to 57 percent when disease was deemed resectable by imaging. Some feel that routine laparoscopy is not cost-effective, and that the few studies relating to its use have many limitations [47]. Other papers suggest specific criteria for when laparoscopy should be used preoperatively, such as for tumors in the pancreatic body and tail [48, 49] and tumors greater than 3 cm [50].



(a) **(b)**

Fig. 9.3 Focal Acute on Chronic Pancreatitis – **(a, b)** Axial plane and curved multiplanar reformatted image of the pancreas shows a pancreatic head "mass," (black arrowheads) a dilated pancreatic duct (white arrows) in the pancreatic body and tail and involutional changes of the pancreatic tail. Pancreatic tail atrophy and ductal obstruction occurs in the setting of proximal obstruction from neoplasm, and can also be seen in chronic pancreatitis. The etiology in this case was determined only by endoscopic ultrasound and biopsy

2.4 Imaging Modalities

Currently, there are multiple imaging modalities for evaluating the pancreas, including multidetector CT, MRI, positron emission tomography, transabdominal ultrasound, endoscopic ultrasound and scintigraphy. Newer techniques being explored include PET/CT and PET/MR fusion, CT perfusion, optical coherence tomography (OCT) and molecular imaging. Expertise in these modalities will vary locally, although there is significant overlap in the information that the modalities can provide.

3 MDCT

CT is the initial imaging test most commonly performed when abnormalities of the pancreas are clinically suspected. Its high sensitivity and specificity for pancreatic disease and non-invasive nature make it a good screening test for malignancy, and it can often assist the radiologist in diagnosing benign pancreatic disease. As the workhorse of abdominal imaging, helical CT and now MDCT have had numerous studies evaluating their use in the setting of pancreatic cancer staging. Generally, CT studies address the detection and characterization of pancreatic tumors, as well as the predictive value of CT for resectability. The most significant problems affecting radiologic imaging, and CT in general, are again in the detection of micrometastatic disease to liver and peritoneum, as well as in the underestimation of vascular invasion [35].

The primary CT sign of pancreatic neoplasm is a focal mass, however focal enlargement of the pancreatic gland is not uncommon in the absence of a discrete visualized tumor. Approximately 10 percent of tumors are not seen by CT because they are isoattenuating to surrounding parenchyma. In these cases secondary signs need to be carefully examined, including ductal dilatation, ductal interruption, pancreatic tail atrophy and abnormal pancreatic contour [53]. When there is isolated pancreatic head enlargement seen on CT, MRI will reveal a focal mass in a significant percentage of these patients [54].

CT has high negative predictive value (NPV) for cancer resectability. In a study of 84 patients with adenocarcinoma, nonresectability was established in 96 percent of cases when helical CT was performed in conjunction with pancreatic CTA [55]. This has been mirrored in several studies, including a study by Lu revealing a 93 percent NPV of CT for pancreatic mass nonresectability [32]. Later MDCT studies have shown high rates of nonresectability as well [56, 57]. When cancer is truly nonresectable radiologists are effective in identifying this. Many of these patients who subsequently undergo laparotomy are, in fact, non-operable due to micrometastases detected at the time of surgery

In primary pancreatic cancer, detection by CT correlates with tumor size [58]. Overall, helical CT has a sensitivity for detection of 76 percent to 92 percent [28]. Prior studies show poor tumor sensitivities for detection of lesions smaller than

2 cm, ranging from 58 percent to 67 percent [58, 59]. A more recent MDCT study improves on these sensitivities slightly, with a sensitivity of 72 percent to 77 percent for tumors < 2 cm [14]. More recent studies including MDCT show higher lesion sensitivity, with improvement in CT technology [60, 61].

CT is effective in the detection of small pancreatic cystic neoplasms, however characterization of these lesions is difficult utilizing this modality. As stated above, there are certain CT signs which are more suggestive of malignancy. Regarding specific lesion characterization, peripheral calcification is a feature typically seen in mucinous tumors. Overall, a blinded retrospective study of 50 patients showed a diagnostic accuracy of CT in separating serous from mucinous neoplasms ranging from only 23 percent to 41 percent [62]. A recent study had more success in distinguishing lesions such as macrocystic cystadenoma from mucinous tumors, including IPMN [63].

In the detection of neuroendocrine tumors the majority of patients have clinical symptoms, however lesion detection still remains difficult. Currently, intraoperative ultrasound has the highest sensitivity for lesion detection at 83 percent and should be considered the gold standard [64] (Fig. 9.4). CT has been shown to be able to detect lesions as small as 4 mm [65]. This study had a sensitivity of 82

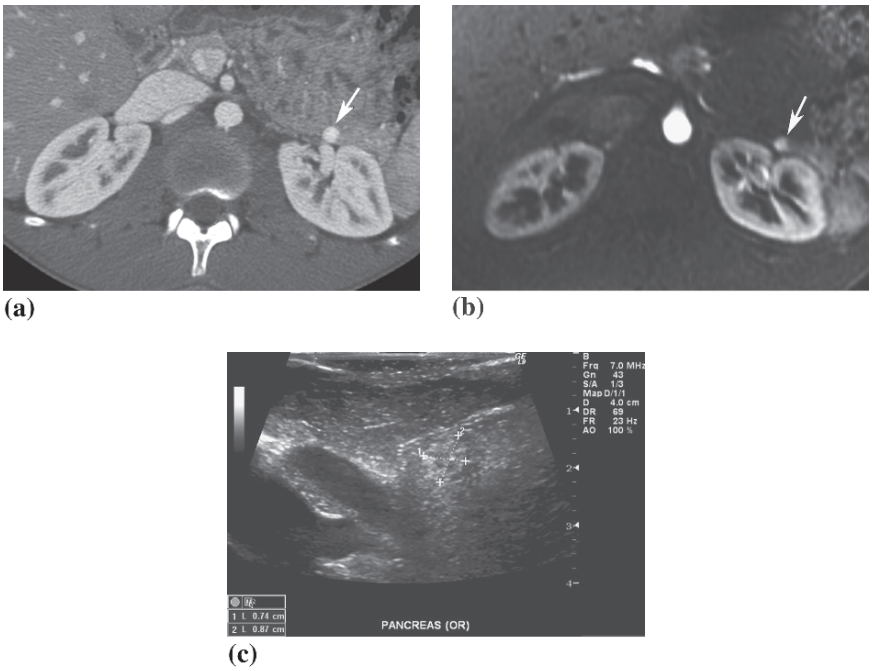


Fig. 9.4 Insulinoma on CT, MRI and intra-operative US. **(a)** Axial contrast-enhanced MDCT image shows a hypervascular mass in the tail of the pancreas (arrow). **(b)** This mass is confirmed by Gadolinium-enhanced MRI (arrow). **(c)** Intra-operative ultrasound has the highest sensitivity for focal pancreatic lesions of these three examinations, and was able to detect this lesion before it was resected

percent for lesions, but two lesions less than 5 mm were not detected. A more recent MDCT study showed a sensitivity of 84 percent [66], which exceeded both EUS (79 percent) and somatostatin scintigraphy (58 percent). In the setting of insulinomas a recent study showed a sensitivity of thin-section MDCT of 94 percent which was equivalent to EUS. Sensitivity of MDCT was significantly decreased when thin sections were not utilized. When CT and EUS were combined, all lesions were detected [67]. Older literature supports the superiority of EUS compared to CT in the detection of small lesions, however as MDCT improves, detection rates will undoubtedly increase. Non-functioning neuroendocrine lesions are typically larger at presentation, and detection approaches 100 percent [68].

4 MRI

MRI is typically used as a problem-solving modality, for example, when a pancreatic mass is suspected, but not identified on MDCT. It should also be considered an excellent imaging study in patients with an iodinated contrast allergy (Fig. 9.5).

Generally, imaging principles of MDCT translate over to MRI, including principles of contrast enhancement (hypervascular versus hypovascular) and spatial resolution. MRI has increased tissue contrast resolution over CT, which is its primary imaging advantage.

Studies reveal that the sensitivity of MRI for cancer detection utilizing contrast is similar, if not better, than that of helical CT [28], however the majority of these direct comparative studies were not performed utilizing MDCT. A recent study comparing MRI, including MRCP to MDCT in the assessment of locoregional

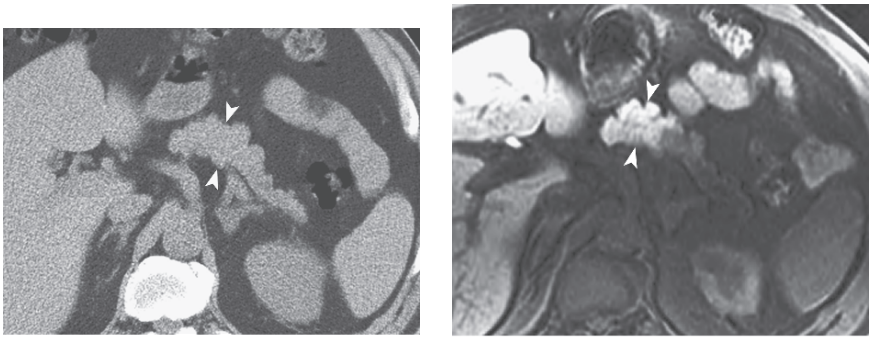


Fig. 9.5 Adenocarcinoma on CT and MRI. **(a)** axial non-contrast CT image shows focal prominence of the pancreatic neck (arrowheads). Note involution of the pancreatic tail which occurs with ductal obstruction. This patient was unable to get a contrast-enhanced CT scan. **(b)** Contrast-enhanced MRI (using Mn-DPDP contrast) shows a focal mass responsible for the pancreatic enlargement (arrowheads). MRI can be utilized as a problem-solving modality

extension, reports that MDCT including MPR images has significantly increased sensitivity for disease over MRI (96 percent versus 83 percent), whereas MRI was only minimally more specific (98 percent versus 97 percent) for disease [72]. This study correctly notes that, due to rapid advances in CT technology, many of the prior comparative studies need reevaluation.

Additionally, an interesting study comparing MDCT to MRI in the detection of subcentimeter hepatic lesions notes that of 178 MDCT detected subcentimeter hepatic lesions, MRI was able to improve on CT specificity of lesions (97.5 percent versus 77.3 percent). Sensitivity of MRI and MDCT for subcentimeter lesions was similar (83.3 percent versus 81.2 percent) [73]. While this study was not without limitations, the specificity and accuracy of MRI may be able to help characterize lesions in cases of suspected liver metastases, especially with the high prevalence of subcentimeter hepatic metastatic disease in patients with known malignancy [74]. Contrast-enhanced MRI has been shown in a separate study to increase detection of hepatic metastases versus CT [75].

In the setting of neuroendocrine tumors, sensitivity of MRI has been reported to be 85 percent. In the setting of hepatic metastases, MRI was shown to outperform CT and somatostatin SPECT with sensitivities of 95 percent, 79 percent and 49 percent, respectively [76]. This is likely due to the higher specificity of MRI, as described above, and the lower spatial resolution of SPECT.

The addition of a diffusion sequence to pancreatic MRI may be sensitive and specific for adenocarcinoma, as demonstrated in a recent study. The authors were able to obtain a sensitivity and specificity of 96.2 percent and 98.6 percent for adenocarcinoma [71]. The smallest tumor in this study was 16 mm and, thus, additional study is required for the detection of smaller tumors using this technique, as well as for its use in the detection of metastatic disease. An effective use could be in the differentiation of adenocarcinoma from chronic pancreatitis, and this sequence only requires a nominal increase in overall study time.

MRCP performed after secretin administration is found to improve the detection of IPMNs. In addition to facilitating the depiction of the morphological characteristics of the lesions, they also help in detection of the communication of the branch duct IPMNs with the main pancreatic duct (Fig. 9.6). Secretin MRCP is fast emerging as the most suitable imaging modality in the diagnosis and follow up of IPMNs of the collateral branches.

5 FDG-PET and PET-CT

F18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a rapidly evolving technique that can detect pancreatic tumors as small as 7 mm in size and additional distant metastases in 40 percent of patients [77].

While FDG-PET can show increased uptake within primary pancreatic tumors, as well as detect metastatic organ and nodal disease, its poor spatial localization does not allow for assessment of vascular invasion. FDG-PET has a sensitivity and

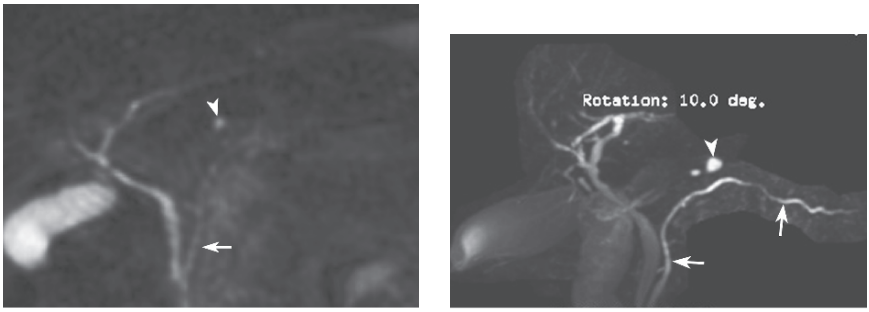


Fig. 9.6 Secretin-enhanced MRCP. **(a)** Pre-Secretin MRCP maximum intensity projection (MIP) image shows the pancreatic duct (arrow) and a focal bright lesion (arrowhead) adjacent to the duct. **(b)** Secretin administration allows for ductal distention allowing for improved visualization. The lesion was shown to connect with the duct (not shown), consistent with side-branch IPMN

specificity for adenocarcinoma detection of 71 percent to 100 percent, and 53 percent to 100 percent, respectively, based on a 2004 metanalysis [78]. Typically, with FDG-PET scans, foci of uptake must be correlated topographically with separately acquired MRI or CT studies (Fig. 9.7). Studies have shown that when CT and FDG-PET are integrated into one machine, diagnostic accuracy in the detection and localization of multiple tumor types is clearly better than with either modality alone [79]. When an integrated PET/CT system is not available, retrospective image fusion techniques can help improve the accuracy and sensitivity of FDG-PET and CT for lesion detection [80]. Retrospective fusion can also be performed utilizing FDG-PET and MR images [81]. An integrated PET/MRI system is on the horizon.

The clinical role of FDG-PET in pancreatic malignancy is to detect unsuspected metastatic disease and to increase the specificity of visualized lesions, especially in the liver. In the detection of liver metastases, one study showed 70 percent sensitivity and 95 percent specificity [82], although another study by the same authors showed that the detection rate fell when lesions were < 1 cm, decreasing from 97 percent to 43 percent [82, 83]. In the detection of nodal metastases, FDG-PET demonstrated a 49 percent sensitivity and 63 percent specificity [82]. Sahani, et al. [84] confirmed that contrast-enhanced liver MRI with a hepatocyte specific contrast agent (Mangafodipir, Amersham Health, Oslo, Norway) was able to detect more metastatic lesions than whole body FDG-PET, especially when under 1 cm. It is still unclear how dual PET-CT would compare to MRI in metastatic lesion detection and characterization. Many institutions do not utilize intravenous contrast in their dual PET-CT studies, and use only noncontrast CT scans for attenuation correction. This lowers sensitivity of the CT portion of the exam for liver metastases, which are most often only evident on contrast-enhanced images.

Yang, et al. did not show a significant difference in the detection of hepatic metastases between FDG-PET and MRI, but conceded that MRI is more specific [85]. This study included tumor sources other than pancreas, which may have favorably altered the FDG-PET lesion detection sensitivity. Microscopic peritoneal

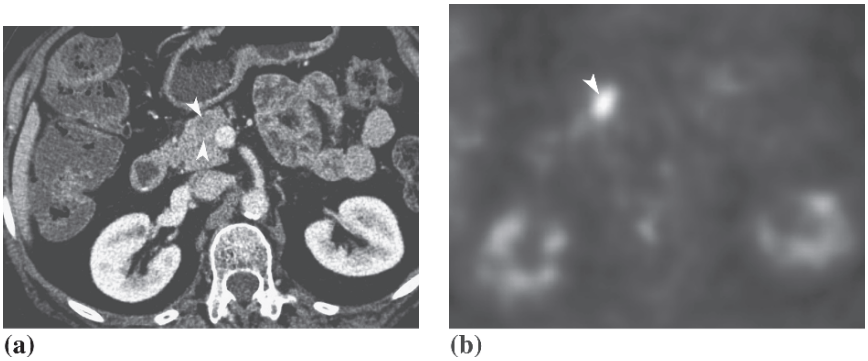


Fig. 9.7 Pancreatic adenocarcinoma on CT and FDG-PET. **(a)** Axial contrast-enhanced CT image demonstrates a focal hypodense mass in the pancreatic head. **(b)** FDG-PET shows focal tracer uptake in the pancreatic head corresponding to the mass. Separately acquired CT and PET images must be "topographically correlated" unless a dual PET/CT machine is utilized. Fusion software can also be used. FDG-PET is more often used as a problem-solving tool, as opposed to initial adenocarcinoma workup at our institution

metastases are beneath the resolution of FDG-PET. One study detected only 25 percent of peritoneal metastases [82].

Other investigations on the clinical utility of FDG-PET focus on therapeutic response and assessment of prognosis in pancreatic adenocarcinoma. The goal of FDG-PET is to separate treatment responders from non-responders, as a cellular response to treatment detectable by FDG-PET can precede morphologic changes by CT. In a small subset of patients undergoing arterial chemoinfusion and external radiotherapy, Yoshioka, et al. demonstrated a lag time in visualized tumor response by CT, with changes detected earlier by FDG-PET [86].

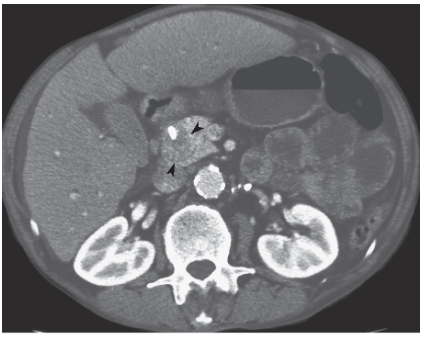
A pilot study by Maisey, et al. showed that a decrease in FDG uptake from baseline to zero after one month of therapy correlated with increased survival [87]. In another study of 93 patients with ductal adenocarcinoma, 15 underwent chemoradiation and were assessed by CT and FDG-PET, both pre- and post-therapy. FDG-PET was superior to CT in assessing tumor response in five of 15 patients, whereas these patients showed no response by CT [88]. Rose, et al. studied the role of FDG-PET in patients undergoing neoadjuvant chemoradiation; six patients showed a change in disease extent that was not detectable by CT [89]. Interestingly, these studies also assessed whether staging FDG-PET studies would change pre-operative management and found it did in 21.5 percent and 43 percent of patients, respectively.

Additional uses FDG-PET in the evaluation of pancreatic neoplasms have been assessed. While cellular uptake of FDG and the acquisition of counts vary slightly, "dual phase" studies have been investigated which allow more time for cells to accumulate tracers before additional uptake values are established. Lychick, et al. showed that combining staging information with ratios of FDG uptake at one and two hours after injection was predictive of patient survival [90]. Another group showed that in delayed scans at two hours, uptake was significantly increased over one hour uptake

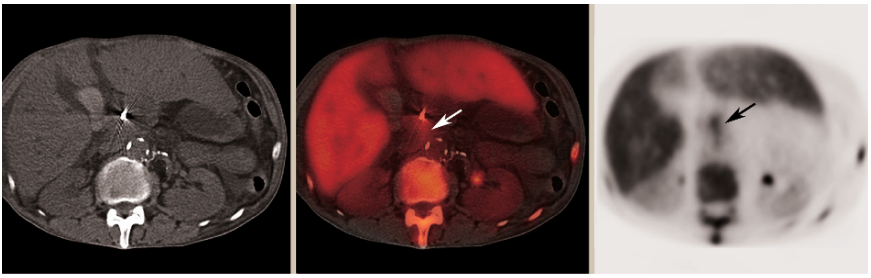
in malignancy [91]. Conversely, cancers can show washout of tracers and have decreased uptake of FDG at two hours [77], thus diminishing the specificity of this sign.

5.1 FLT-PET

While FDG-PET has variable specificity for different diseases, attempts to improve on specificity are currently being studied, especially in the role of distinguishing between adenocarcinoma and chronic pancreatitis. 18F-flouro-3'deoxy-3'-L-fluorothymidine (18F-FLT) is a proliferation tracer which is phosphorylated by thymidine kinase 1, and is incorporated into cells which utilize a salvage pathway for DNA synthesis. 18F-FLT-PET, compared with 18F-FDG-PET, has shown to be less sensitive for disease than FDG-PET in multiple studies utilizing various cell lines and different neoplasms [92]. For example, FLT-PET shows significant liver and bone uptake, limiting its utilization for detection of metastases to these organs. FLT-PET, however, is more tumor-specific than FDG-PET [93], and its role in evaluating pancreatic cancer is currently being studied (Fig. 9.8). Since 18F - FLT is not



(a)



(b)

Fig. 9.8 Pancreatic adenocarcinoma on FLT-PET. **(a)** axial contrast-enhanced MDCT image through the pancreas shows a focal hypodense obstructing mass in the pancreatic head which was stented (arrowheads). **(b)** FLT-PET image (left to right: non-contrast CT, fused non-contrast CT / FLT-PET, FLT-PET image only) shows avid tracer uptake in the pancreatic head (arrows). This technique may be more tumor-specific than FDG-PET, although notice that significant liver and bone tracer uptake limits sensitivity for tumors in these organs

directly incorporated into DNA, new analogues are being created that would be incorporated, perhaps more accurately reflecting cellular turnover [92].

In the setting of cystic pancreatic lesions, a recent study has shown that the sensitivity of FDG-PET was 57 percent and specificity 85 percent for malignancy [94]. In the FDG-PET-detected malignant lesions, cross-sectional imaging was able to detect malignant features and, thus, PET only confirmed these findings and did not aid in the detection of occult malignancy. Therefore, the authors have suggested that PET does not play a role in determining malignancy in pancreatic cystic lesions.

6 Transabdominal Ultrasound

The utility of transabdominal ultrasound in the diagnosis of pancreatic cancer in the United States is limited. Limiting technical factors often relate to large patient habitus and overlying bowel gas. Additionally, in the United States, ultrasound technologists are the primary imagers performing the examinations [95].

Contrast-enhanced ultrasound, with intravenously injected microbubbles, is utilized in Europe as an alternative to more expensive imaging modalities such as EUS and MRI. Although histology is the reference, there are ultrasound characteristics suggestive of various tumor types [96]. While contrast-enhanced ultrasound deserves attention, it is currently not approved for clinical use in this country. Interesting research is underway that will target microbubbles to specific pancreatic tumor vasculature. Antibodies against tumor vasculature can be synthesized, conjugated to microbubbles, and then imaged by ultrasound [97].

7 Endoscopic Ultrasound (EUS)

Endoscopic ultrasound clearly has a role in current diagnosis and staging of pancreatic abnormalities. Aside from tumor detection, EUS-guided FNA may be indicated when tissue sampling is required prior to adjuvant or palliative therapy, or when the diagnosis of carcinoma versus inflammatory disease is unclear.

EUS is superior to MDCT in the detection of pancreatic lesions less than 2 to 3 mm, with a sensitivity of > 90 percent [98] for lesions this size. A recent metanalysis by DeWitt showed that studies comparing EUS and MDCT have intrinsic limitations, and that newer studies incorporating advances in imaging are required [99]. Nonetheless, EUS and MDCT appear to be similar for assessing local extension and tumor respectability, and in detecting nodal disease. An additional advantage of EUS is that fine needle aspiration can be performed at the time of study (Fig. 9.9). This technique has a negative predictive value that approaches 100 percent [100], although pathology results are dependent on pathologist experience [101], and a recent metanalysis showed an overall 88 percent sensitivity and 96 percent specificity of EUS for cancer in solid pancreatic masses [102]. Additional work is being performed assessing the use of EUS in the local administration of chemotherapeutic agents [103]. Palliative celiac neurolysis can be administered by EUS [104], although this technique is also

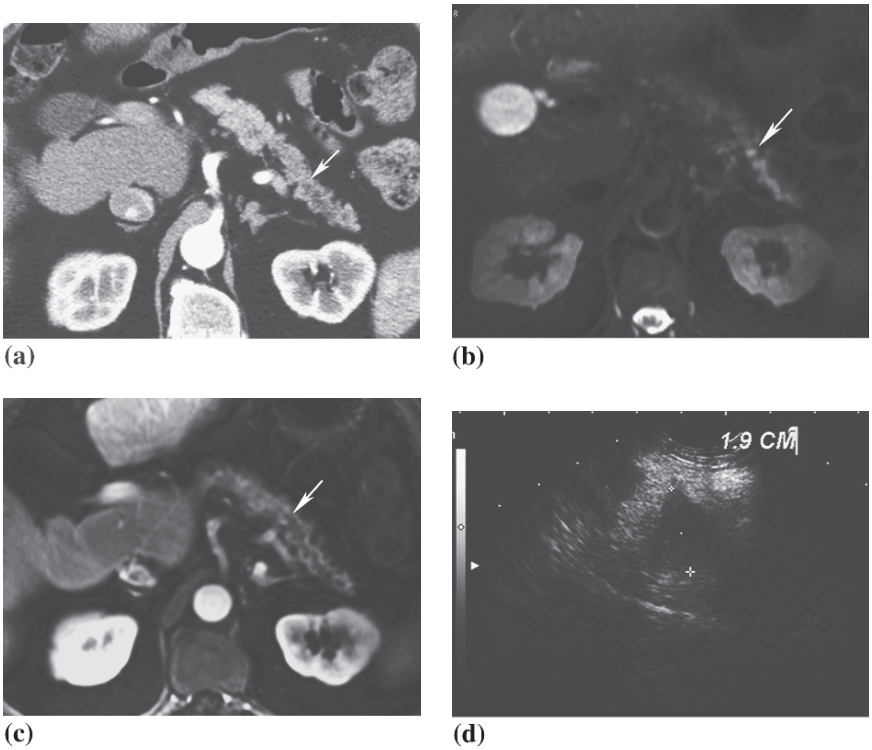


Fig. 9.9 Acinar cell neoplasm on CT, MRI, and EUS **– (a)** Axial image from a contrast-enhanced MDCT of the pancreas shows a dilated pancreatic duct in the tail, without a clear focal obstructing mass (arrows). **(b, c)** T2 and T1 post-Gadolinium axial MR images mirror the CT scan findings of a dilated duct. Again, no focal mass is seen. **(d)** Endoscopic ultrasound revealed a 1.9 cm obstructing mass. This was biopsy-proven acinar cell neoplasm

straightforward utilizing CT-guided techniques [105]. Other EUS-guided treatment options, including tumor ablation, are being explored [102].

A reasonable approach is to avoid the use of EUS in the presence of known metastatic disease, unless tissue diagnosis is required for treatment. If a suspicious pancreatic mass is present on MDCT and the clinical context is correct, the patient can proceed to surgery if the tumor is deemed resectable. Given the high sensitivity for small lesions, EUS can be performed if the CT shows a focal abnormality without a clear mass, or if ductal signs suggest an infiltrative process and there is a suspicion for chronic pancreatitis [102]. In summary, as EUS is unable to detect distant disease, conjunction with other cross-sectional modalities is necessary for its use.

EUS is excellent in the detection of neuroendocrine lesions with a sensitivity and specificity of 93 percent and 95 percent [106], however FNA is needed to make the diagnosis at the time of exam. This is especially useful in the setting of insulinomas, which are not easily seen at scintigraphy [13], and if they are also not detected by CT or MRI.

8 Endoscopic Retrograde Cholangiopancreatography (ERCP)

This modality is currently utilized for obtaining high resolution images of the pancreatic duct, and is considered the gold standard for evaluating the pancreatic duct [107]. ERCP can also be utilized for several purposes, including endoscopic sphincterotomy, removal of stones, as well as the insertion of stents and dilation of biliary or pancreatic strictures.

ERCP has high sensitivity and specificity for cancer, and is useful in detecting tumors if there is main pancreatic ductal involvement. When the main pancreatic duct is dilated in the setting of side-branch IPMN (mixed type) or in isolation (main duct type), this technique can confirm the findings of IPMN and exclude other causes of ductal dilatation, such as stricture from chronic pancreatitis. Focal uncinate or tail lesions can be missed if they do not involve the main pancreatic duct. In the setting of obstruction, ERCP is usually considered a palliative procedure. Comparisons of ERCP and EUS-guided FNA for the evaluation of biliary strictures has shown that EUS is superior to ERCP [102].

It should be noted that newer techniques such as intraductal ultrasonography, pancreatoscopy and optical coherence tomography can be performed using ERCP hardware [108]. New technology may allow the ERCP and EUS scope to be combined into one instrument (also known as EURCP) to provide both diagnostic and therapeutic techniques in the same setting, although these studies are currently often performed sequentially.

9 Intraductal Ultrasound (IDUS)

The use of a 2 mm probe fed into the pancreatic duct during ERCP over a guidewire can help to detect focal ductal lesions < 1 mm in height. This technique differs from EUS and transabdominal US in that a high frequency probe is utilized to maximize tissue resolution [108]. A limitation of this technique is when a tight ductal stricture does not allow cannulation of the duct.

In one study comparing IDUS to standard ERCP, EUS and MDCT, the authors showed that IDUS is more sensitive and specific in identifying the cause of strictures than either of the other techniques (100 percent sensitivity, 93 percent specificity for cancer). The other modalities – ERCP, EUS and CT – were 86 percent, 90 percent and 67 percent sensitive, and 67 percent, 58 percent and 67 percent specific for cancer [109]. This author, in another larger study, showed similar values in the detection of pancreatic cancer [110].

10 Optical Coherence Tomography (OCT)

This is a newer technique utilizing existing ERCP hardware for evaluation of ductal epithelium. The probe can be added to an ERCP accessory port and, thus, adds only a short amount of time to the procedure after cannulation of the pancreatic duct. This examination is similar in principle to ultrasound, except that light is utilized for imaging

instead of sound waves [111]. Visualization of the pancreatic duct epithelium directly utilizing infrared light is able to detect changes in epithelial architecture relating to interruption of the normal ductal epithelium. This optical technique allows pancreatic duct mucosal and submucosal structures to be evaluated to a depth of 1 to 2 mm.

While earlier studies were able to differentiate tumors from normal epithelium [112], a more recent study was not able to distinguish tumors from other inflammatory and non-neoplastic ductal conditions [113]. Further research by the authors has been able to differentiate changes in ductal epithelium in chronic pancreatitis from neoplastic disease [114] and, should this prove to be true with further investigation, this exciting prospect may significantly change pancreatic imaging in a small subset of patients. Accuracy for malignancy detection by OCT was 100 percent versus only 67 percent for positivity of brushings in an in vivo study of 15 patients.

11 Scintigraphy

Nuclear medicine detection of hormone secreting lesions such as gastrinoma, insulinoma and other tumors of pancreatic endocrine origin is possible utilizing gamma or other photon-emitting substances coupled to a substance that binds to lesion receptors. Octreotide and Pentetreotide are somatostatin analogues that bind to somatostatin receptors, and are found on many different neuroendocrine neoplasms. These can be bound to Indium-111, which decays and emits photons that can be detected by a gamma detector. [Octreotide (Sandostatin, Novartis Pharmaceuticals), Pentetreotide (Octreoscan, Malinkrodt)].

Previously we stated that neuroendocrine lesions less than 2 cm are not consistently detected by cross-sectional imaging. This is because a significant percentage of these lesions are not located in the pancreas proper. For example, occult Gastrinomas are often located in an area called the "Gastrinoma triangle," defined by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly and the junction of the neck and body of the pancreas medially [117].

Sensitivity varies on the type of tumor being imaged, however one study assessing gastrinoma showed a 58 percent lesion sensitivity with scintigraphy, which was better than all other modalities (CT, MRI, US). In fact, the other modalities only increased the overall detection rate to 68 percent [118].

11.1 Emerging Technologies: Molecular/Angiogenesis Imaging

While lesion detection by imaging continues to approach the histologic and surgical standard, we note that the spatial resolution of the above modalities is only on the order of millimeters in the best possible scenario. Detecting changes of panIN and precursor lesions will require novel approaches that exploit cellular abnormalities, such as alterations in cellular receptor sites.

For example, utilizing a mouse model, one set of researchers were able to utilize a magneto/fluorescent nanoparticle conjugate that was targeted to bombesin receptors of pancreatic ductal cells [119]. Pancreatic ductal adenocarcinomas, unlike normal pancreatic ductal cells, do not express this binding receptor [120]. The experimental model was able to demonstrate a decrease in MRI T2 signal intensity in normal pancreatic tissue, thus increasing signal intensity of the pancreatic tumor and the affected pancreatic specimen. Translation into clinical imaging may be promising. Numerous other molecular agents are in development to increase the sensitivity and specificity of MRI, as well as other imaging.

Research has shown that tumor growth is dependent on the production of a vascular network beyond 2 mm^3, and numerous growth factors that regulate this, such as vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), fibroblast growth factor (FGF) as well as interleukins (IL) have been demonstrated [121]. Anti-angiogenesis agents are in development, and the ability to monitor tissue perfusional changes before macroscopic changes are evident will be critical in patient management.

11.2 CT Perfusion

Utilizing a workstation and imaging software, one can dynamically assess tumoral bloodflow and monitor response to chemotherapy and radiation changes using bloodflow and tissue perfusion parameters. Since adenocarcinoma of the pancreas is hypovascular compared to normal pancreatic parenchyma, the tumor would involve an area of hypoperfusion, compared to normal pancreatic tissue. CT perfusion measurements of pancreatic tissue have been shown to be technically feasible [122]. A recent study from China has also shown the utility of pancreatic CT perfusion in the characterization and detection of insulinomas, a typically hypervascular tumor [123]. These lesions show increased blood flow and blood volume, compared with normal pancreatic tissue. Perfusion CT of the pancreas is an exciting and emerging technique which demands further study.

11.3 Dynamic Contrast-Enhanced MRI (DCE-MRI)

Similar to perfusion CT, tissue perfusion and permeability can be assessed before, during and after contrast administration. Tissue parameters as measured by T1 and T2 signal characteristics can be quantified by the use of imaging software. The main use for this technique has been in the development of anti-angiogenic drugs, however DCE-MRI has shown some difficulty with reproducibility across trials, and issues of reliable measurements in heterogeneous tumors have been noted. Further validation is also needed regarding protocol design [121, 124]. It should be noted that a study by Johnson, et al reported that this technique was unable to distinguish between chronic pancreatitis and cancer [125].

11.4 Conclusion

When pancreatic neoplasm is suspected, there are a large number of imaging modalities available which should be viewed as complementary. MDCT imaging should be considered as the initial imaging study, regardless of suspected tumor type, with MRI utilized for further lesion characterization and to increase specificity in the setting of cystic pancreatic lesions and small liver lesions. When clinically apparent lesions are not detected, EUS should be utilized for troubleshooting and tissue diagnosis, due to its high sensitivity for local disease, with ERCP utilized for palliative stent placement as necessary. When hormonal syndromes suggest a neuroendocrine tumor, and if CT does not detect the lesion, scintigraphy should be performed before the patient has localization by EUS or intraoperative ultrasound, as it is non-invasive. Additionally, it should be noted that operative techniques such as laparoscopy and ultrasound have a high sensitivity for disease and, thus, can play a role in conjunction with imaging.

Current challenges include avoiding excessive imaging in patients with incidentally detected cystic lesions, increasing early detection in aggressive disease with more tumor specific imaging and improving staging accuracy without increasing the amount of imaging needed to do so. There are numerous unresolved issues in the world of pancreatic tumoral imaging, however new research in tumor pathogenesis will hopefully add to patient care, and eventually improve survival in those patients with advanced disease.

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