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PET-CT for pancreatic malignancy: potential and pitfalls.

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Abstract

Pancreatic malignancy carries a poor prognosis and is the 4th leading cause of cancer related deaths in the United States. While conventional imaging with CT and MR remain the main imaging modalities, recent times have seen an increase in the applications of PET-CT in evaluation of pancreatic malignancy. Newer data is becoming available highlighting the advantages, limitations and pitfalls in PET-CT imaging of the pancreas. This article highlights the applications of PET-CT in various stages of management of pancreatic malignancy, compares these with conventional imaging with CT and MR.

Keywords: Pancreatic malignancy, pancreas adenocarcinoma, PET-CT, PET-MR, pancreatic adenocarcinoma.

Introduction

Pancreatic malignancy is a heterogeneous group of neoplasms. 85% of malignant tumors are of exocrine origin including ductal adenocarcinoma and the rare acinar cell carcinoma (1-2%). Less common cystic neoplasms include serous and cystic pancreatic tumors (1-2% each) and intra-papillary mucinous neoplasms (3-5%). Epithelial and mixed differentiation tumors consist of solid pseudopapillary neoplasms (1-2%), neuroendocrine tumors (1-2%) and pancreatoblastoma (<1%) (*1*).

Pancreatic adenocarcinoma has a poor prognosis, being the 4th leading cause of cancer deaths in United States (*2*). Overall incidence is 12.2 cases per 100,000 persons per year and it usually presents late with 5-year survival rate of 6% at the time of diagnosis (*3,4*). Complete resection is the only cure but only 20% of patients have potentially resectable disease at the time of presentation (*4*). Even patients with resectable disease enjoy a survival rate of approximately only 23% (*2, 3*).

Contrast enhanced CT (CECT) is the most widely utilized modality in the work-up of pancreatic malignancy. Traditionally, computed tomography (CT), transabdominal ultrasound (US), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), positron emission tomography (PET), and PET-CT, have been applied to image pancreatic processes (Table 1). Newer data substantiating an emerging role for PET-CT has been published recently.

PET-CT application in Initial Management of Pancreatic Malignancy

Most malignant tumors are hypermetabolic compared to the normal pancreas, which demonstrates minimal to no FDG uptake (Figure 1, Supplemental figure 1). Occasionaly, the desmoplastic reaction associated with pancreatic adenocarcinoma may cause the lesion to appear hypometabolic (*5*). 18(18F) fluorodeoxyglucose (FDG) is the most widely clinically utilized radiotracer. Novel

radiotracers, which provide greater specificity for detecting malignant processes, for example, sigma-receptor ligands and 18F-3′-fluoro-3′-deoxy-l-thymidine, may be helpful in distinguishing tumor recurrence from inflammatory and fibrotic entities. This is secondary to overexpression of thymidine in cancer cells (*5*). The degree of FDG uptake is directly proportional to lesion size, particularly with most lesions larger than one centimeter. Measuring SUV values for tumors smaller than 1 cm is fraught with errors due to partial volume averaging (*6*).

Current recommendations include performing CT or MRI, particularly, contrast-enhanced CT for evaluating patients with clinically suspected pancreatic cancer (*7,8,9*). Multiphase CT or MR is also considered appropriate for suspected pancreatic neuroendocrine tumors (*10*). Recent data supports the role of PET-CT in the initial management for known or suspected pancreatic malignancy, particularly for characterization of lesions, staging disease, pre-surgical and pre-radiotherapy planning.

Isodense or isointense lesions, which are occult on conventional imaging may be detected with PET-CT (Supplemental Figure 1) (*2*). The detection of such lesions on PET precedes that with CT or MR as the hypermetabolism associated with tumors can occur before anatomic alterations are evident (*11,12*). PET-CT and CECT have been shown to have equivalent sensitivity and specificity in diagnosing pancreatic cancer (89–91% *vs* 88%, respectively) (*13,14*).

PET-CT was first used to differentiate chronic pancreatitis from pancreatic malignancy. With chronic pancreatitis, the organ demonstrates diffuse but lower FDG uptake versus more focal uptake and higher Standardized Uptake Value max (SUVmax) seen with tumor involvement (*1,15*). Differentiating mass forming pancreatitis from pancreatic adenocarcinoma remains a diagnostic dilemma, even with CECT, especially given the fibrosis that can accompany both of these processes.

Additionally, adenocarcinomas commonly obstruct the pancreatic duct causing secondary distal pancreatitis, further confounding the diagnosis. Chronic pancreatitis is also a well-known risk factor for adenocarcinoma with 20% lifetime-risk by the age of 60 years, further confounding the diagnosis (*16*). PET-CT offers better characterization of mass forming pancreatitis from adenocarcinoma than CECT (*6,13,15*), based on the distribution and degree of FDG uptake. SUVmax of malignant tumors is usually significantly higher than that of benign lesions, including chronic pancreatitis. Schick et al demonstrated sensitivity and specificity of 89% and 74%, respectively, for PET-CT in differentiating mass forming pancreatitis from malignancy (*6*). Other authors have demonstrated mass lesions without FDG uptake at PET-CT, representing mass forming pancreatitis (*13*).

Lesion size is an important consideration; lesions less than 2 cm in size are often ill-defined, even with CECT (*17*). Some studies suggest that PET-CT can better depict these lesions with Okano et al reporting sensitivities of 100% for PET and 40% for CECT for depicting pancreatic lesions smaller than 2 cm (*18*). Fused contrast-enhanced PET-CT has been proven to be more sensitive for tumor depiction than PET or CT alone by Lemke et al (*19*).

PET-CT plays an important role in evaluating *poorly differentiated* NETs and differentiating benign versus malignant cystic neoplasms such as IPMNs (*20,21*). Highly differentiated and hormonally active NETs are often FDG-negative and octreotide positive, however, the poorly differentiated NETs are mostly FDG-positive and octreotide negative secondary to their high proliferative rate, hence, detectable with PET-CT (20). PET-CT was proven to be highly sensitive and accurate in distinguishing benign from malignant IMPNs with mural nodules, 3 mm or greater in size (*21*). The specificity and PPV were also high noted to be 100%, using SUV max cutoff value of 2.3 (*21*).

Imaging guided biopsies can be targeted precisely using information available from PET-CT (Figure 1). Targeted biopsy of the most hypermetabolic portion of the tumor can lead to higher diagnostic yields, which is particularly important in heterogeneous tumors with necrosis; tumors with significant cystic components and with equivocal results of CT guided biopsies (*5,22*). Specifically for

pancreatic cancers, inflammatory and desmoplastic reactions associated with the tumor may be indistinguishable from the primary mass itself on conventional imaging (*5,22*). Therefore PET-CT can play a part in targeting the most FDG avid portions of the tumor, aiding tissue diagnosis.

PET-CT application in staging and pre-surgical planning

Determination of resectability is the cornerstone of treatment planning for pancreatic tumors. An ideal imaging modality should be able to detect nodal and distant metastases (Figure 2, Figure 3, Supplemental Figure 2) and invasion of adjacent critical neurovascular structures including superior mesenteric artery and vein, portal vein, celiac, hepatic and gastroduodenal arteries. While most of these criteria are fulfilled by CECT (*23*), PET has a superior performance in the initial staging disease, mostly secondary to detection of nodal and distant metastases.

Locoregional spread

Assessing the local tumor spread is crucial in staging pancreatic malignancy and in deciding for potentially curative respectability. Lymph node staging is suboptimal with CT and has 37% sensitivity and 79% specificity (Figure 2) (*24*). Using traditional criteria of nodal measurements of more than 1cm in short axis doesn't adequately differentiate between benign and malignant processes. Lymph nodes smaller than 1cm have been shown to be eventually malignant in nature. PET-CT allows for moderate advantage over CECT by demonstrating FDG uptake within these equivocal or non-enlarged nodes (*5*). Asagi et al report accuracy of 42% for lymph node metastasis (*25*). However, even PET-CT may remain inadequate with cases of low tumor burden in the nodes or due to strong photon scatter from an avidly hypermetabolic primary mass, so-called penumbra effect (*5, 13, 14*).

Distant metastases

Pancreatic malignancy most commonly metastasizes to the liver and to the peritoneum (Figure 3,

Supplemental Figure 2, Supplemental Figure 3). PET-CT, even without contrast, is reportedly more sensitive than conventional CT (88–91% *vs* 30–57%, respectively) in identifying distant metastases (*13,14*). Detecting isodense liver lesions, particularly in the setting of chemotherapy induced steatosis, is difficult with CECT secondary to masking of these hypodense metastases over a background of hypodense liver parenchyma. Foci of hypermetabolism in these otherwise occult lesions strongly points to the presence of metastases (*13*). CT at best has a moderate sensitivity (65%–88%) and specificity (38%–63%) for detecting peritoneal metastatic implants (*26,27*). Peritoneal metastases may be found at staging laparoscopy in up to 7% of patients with locally unresectable pancreatic cancer without any evidence of metastasis at CECT (*26,27*).

PET-CT was demonstrated to be more accurate and sensitive in diagnosing primary pancreatic tumor and metastases, when compared with CECT, and MRI/MRCP (*13*). In this study performed by Kauhanen et al, PET was superior in initial staging in 10 of 38 and had a reported sensitivity of 88%. However, limitations persisted in diagnosing lymph node metastases (*13*).

PET-CT makes the most impact in initial staging of pancreatic adenocarcinoma by detecting small metastases and distant metastases (Figure 2, Figure 4, Supplemental Figure 2). The performance of PET compared to that of CT, transabdominal US, and endoscopic US in diagnosing adenocarcinoma found superior sensitivity and specificity of PET at 96% and 78%, respectively. Same values for other modalities were reported in the current literature as follows: CT (91% and 56%), transabdominal US (91% and 50%), and endoscopic US (96% and 67%) (*20*). Barber et al demonstrated benefits of PET-CT over conventional imaging by detecting distant metastases and preventing unnecessary laparotomy. Based on PET-CT results management was altered in 41% patients in their cohort (*28*), of which 33% occurred at initial staging, and 43% patients at subsequent imaging, all secondary to upstaging disease (Figure 4) (*28*). However, classic pitfalls such as misregistration of liver metabolism mimicking as lung nodules (Figure 5) and diffuse bone marrow uptake after chemotherapy (Supplemental Figure 4) should be realized to prevent erroneous staging of the disease.

For assessing for pre-operative resectability, however, contrast-enhanced PET-CT has been studied to be superior to PET alone (*29*). PET and PET-CT both had sensitivities of 100%, however contrast-enhanced PET-CT was superior to unenhanced PET-CT (sensitivity of 96% and a specificity of 82%). In this study by Strobel et al, 10% of patients had unresectable tumors diagnosed intraoperatively, which were missed with all imaging modalities. These included 2 liver metastases, 1 peritoneal carcinomatosis and 2 cases of mesenteric root invasion. All cases of arterial invasion were accurately depicted by contrast enhanced PET-CT. Contrast-enhanced PET-CT picked up more distant metastases (90% *vs* 67% *vs* 43%), peritoneal carcinomatosis (80% *vs* 60% *vs* 20%), and arterial infiltration (100% *vs* 0% *vs* 0%) than that of noncontrast PET-CT and PET alone, respectively (*29*).

PET-CT applications in pre-radiotherapy planning

PET-CT is helpful in estimating tumor volume and planning the conformal radiation field in candidates for radiotherapy, with improved delineation of tumor margins compared to CT alone (*1,30*). A single-institution experience of adding PET to CT resulted in approximately 30% increase in gross tumor volume, owing to incorporation of additional nodal metastases and extension of the primary volume beyond that defined with CT (*31*).

PET-CT applications towards prognosis, response to therapy, recurrence and subsequent management

Schellenberg et al proved that SUV values obtained alone from pretreatment PET-CTs were prognostic of overall survival and progression-free survival in patients with unresectable pancreatic cancer even when controlled for age, presenting CA19-9 levels, and single versus combination chemotherapy (*32*). The higher the baseline SUVmax value, the greater the likelihood of recurrence in early postoperative period. SUVmax may also be independent predictor for overall survival in patients with locally advanced pancreatic cancer (*32,33*). In a study performed by Sperti et al, at 1-year follow-up, none of the patients with a SUV greater than 4.0 had survived, and 75% of those with

a SUV less or equal to 4.0 were still alive (*34*). At least 6 weeks waiting period is recommended after an intervention or radiation to limit false positive FDG uptake secondary to inflammation from these procedures (*35*,*36*).

Reduced FDG uptake may precede actual morphological changes, allowing for increased sensitivity of PET-CT in assessing disease recurrence and response to therapy (Supplemental Figure 6). Pre- and post chemotherapy PET-CT can be compared to estimate the degree of chemotherapeutic effect and hence, predict survival (*37*). PET-CT has been shown to improve evaluation for cancer recurrence, particularly, in patients with elevated CA19-9 levels and those with normal or equivocal CT findings. Tissue remodeling associated with healing may hinder the assessment of treatment response on CT. Studies have noted a correlation between the variations observed in the SUV before and after radiochemotherapy and tumor necrosis. Reportedly, decreased FDG uptake after radio-chemotherapy without definite response on CT may allow for subsequent surgical resection (*38*).

PET is more sensitive than CECT for monitoring response to chemoradiation and depicting tumor recurrence after surgery (*34*,*35*,*37*,*39*). Vast majority (72-92%) of pancreatic adenocarcinomas recur locally within 2 years of surgery (*34*). Delineating postsurgical architectural changes from recurrent tumor is limited, even on CECT. This may be better clarified, if these findings are associated with hypermetabolism, suggesting recurrence (*6*,*34*). Postoperative FDG uptake in the surgical bed is expected to resolve by 3 months after surgery and any remaining uptake after this time is usually indicative of residual tumor or recurrence. The functional capabilities of PET make it highly (96%) sensitive in depicting tumor recurrence compared to 39% sensitivity for CT and MRI (*35*). For the same reason, tumor relapse is also detected earlier with PET than CT, with higher sensitivity (98%) and specificity (90%) (*34*). Ruf et al. (*38*) noted markedly superior sensitivity of PET-CT for detecting recurrence after surgery (96%) compared to 39% with CT or MRI (Figure 6, Supplemental Figure 4) (39%).

Limitations of PET-CT

Both false-positive and false-negative scenarios are associated with PET-CT imaging. False negative

results can be seen with hyperglycemia, a common feature of pancreatic disease, secondary to reduced FDG uptake resultant from competitive inhibition (*20,38*). False-negative cases may also occur in mucinous tumors (due to tissue hypocellularity); necrotic tumors and liver and peritoneal metastases smaller than 1 cm (*20,38*). False positive cases may also result technical reasons such as misregistration of FDG uptake (Figure 5) and attenuation over-correction artifact (Figure 6). Partial volume averaging may lead to erroneous measurement of SUV values in smaller tumors and in tumors located adjacent to areas of high physiologic uptake (*20*). Periampullary tumors are an example of this phenomenon, due to their small size at the time of clinical presentation and proximity to FDG-avid bowel (*20*).

Pancreatic malignancy most commonly metastasizes to the liver and peritoneum (*20*). Identifying these lesions is key towards the most appropriate treatment. However, smaller lesions, below the size threshold of 1 cm, are reportedly most commonly underdiagnosed (*39*). Small lung metastasis can also be overlooked on PET but detected on the CT component of the exam, supporting the complementary nature of the two modalities (*27*).

Tumor mimicking hypermetabolic foci may occur with inflammation such as, acute flare-up of chronic or autoimmune pancreatitis, recent radiation therapy, recent surgical incision and biopsy, and around CBD stents (*20,38*). CECT has a higher spatial resolution than PET-CT. Along with the presence of IV contrast; vascular invasion is better assessed at CECT than unenhanced PET-CT (*38*).

Future directions

Novel PET radiotracers such as 18F-3′-fluoro-3′-deoxy-l-thymidine (FLT) are under development towards clinical application. Thymidine based radiotracers may offer higher specificity, as thymidine, has higher specificity for tumor cells compared to glucose, which is ubiquitous in the body. Tumor cells are known to overexpress sigma-ligand based thymidine receptors and hence selectively uptake FLT. Role of thymidine based tracers in pancreatic malignancy still need to be fully evaluated and further studies are needed.

PET-MR is an additional tool that takes advantageously combines of high soft tissue resolution of MR with functional information of PET. Lack of radiation with MR imaging is a lucrative benefit, especially for patients undergoing frequent imaging. MR may be able to dectect subtle and small lesions, which may be occult on CT. Multiple sequences including T1, diffusion- weighted imaging have been evaluated for potential applications. Tatsumi et al demonstrated improved characterization of pancreatic tumors with PET/MRI fusion, especially PET with T1-w MRI, compared to PET/CT by offering better mapping and fusion image quality (*40*).

Summary

In summary, PET-CT is an advantageous tool in the management of pancreatic cancer. The combination of functional and anatomical data provides a closer depiction of the biological behavior of the tumor, compared to other conventional imaging modalities. PET-CT outperforms all imaging modalities in detection of distant metastases, allowing for more accurate staging, despite its limitations in locoregional assessment for lymphadenopathy and vascular invasion. Limited spatial resolution of PET has been overcome by the CT component of the evaluation and PET complements the lack of functional information on CT. Development of novel tumor specific PET tracers such as the thymidine based radiotracers (FLT) and sigma ligand receptors will allow for further growth of this modality.

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Figures and Figure legends:

Figure 1: Initial staging PET-CT in a 59 year old male with pancreatic mass of unknown etiology. (a) Axial fusion PET-CT fusion images demonstrate a centrally necrotic mass with a hypermetabolic peripheral rim. (b) Axial procedural CT image demonstrates targeted biopsy in progress. PET-CT was used to target the hypermetabolic rim to increase diagnostic confidence.

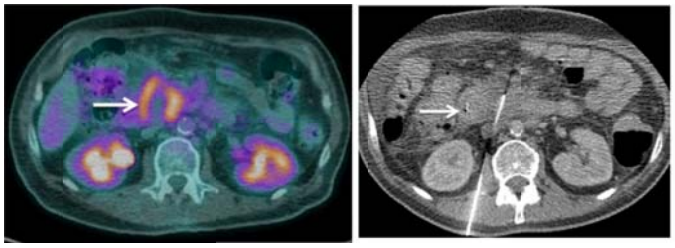

Figure 2: Initial staging PET-CT in a 65 year old male with known pancreatic adenocarcinoma: (a) Axial noncontrast CT demonstrates enlarged mesenteric lymph nodes (circle). (b) Corresponding PET-CT fusion image demonstrates intense FDG uptake within the nodes suggestive of metastatic involvement. Physiologic uptake is present within small bowel.

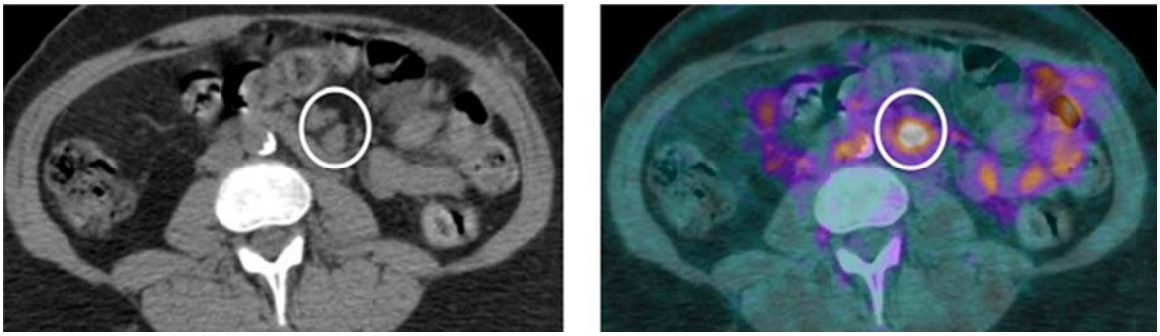

Figure 3: Initial staging PET-CT in a 63-year-old female with pancreatic adenocarcinoma: (a) Noncontrast axial CT images demonstrates ill-defined peritoneal masses within the pelvic cul-de-sac (arrow). This is another difficult location to evaluate with CT alone. (b) Corresponding PET-CT image demonstrates these masses to be intensely hypermetabolic (arrow), helpful in diagnosing peritoneal/mesenteric metastases. Incidental note is made of a fat density mass (circle) within the left adnexa, which doesn't demonstrate any FDG uptake consistent with a dermoid/mature cystic teratoma.

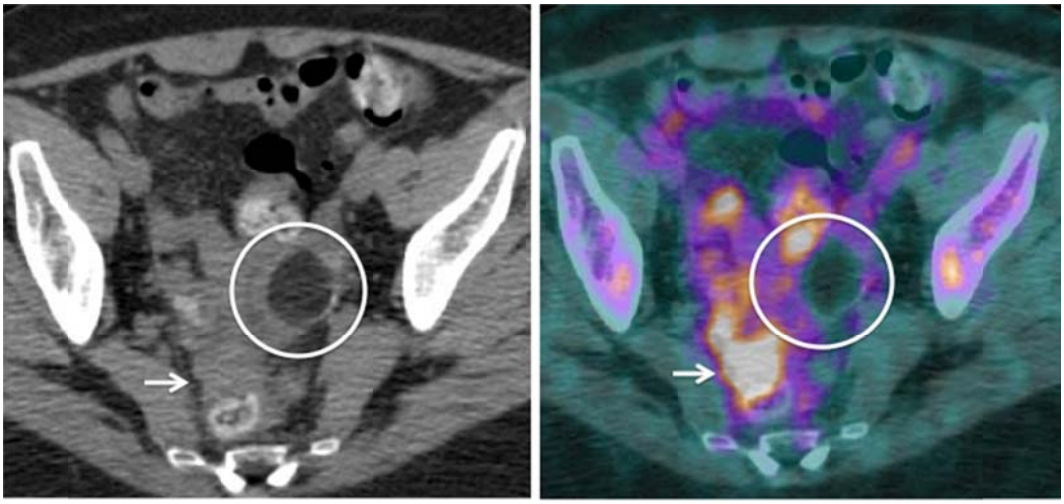

Figure 4: PET-CT performed for evaluating response to chemotherapy in a 69-year-old male with pancreatic adenocarcinoma. (a) Non contrast CT shows a small pleural-based mass adjacent to left lung apex (arrow). (b) Corresponding PET-CT demonstrates its hypermetabolic nature, suggestive of a pleural metastasis. This was previously not identified on contrast enhanced CT and presence of FDG uptake led to improved identification, and hence, more accurate staging assessment with a PET-CT.

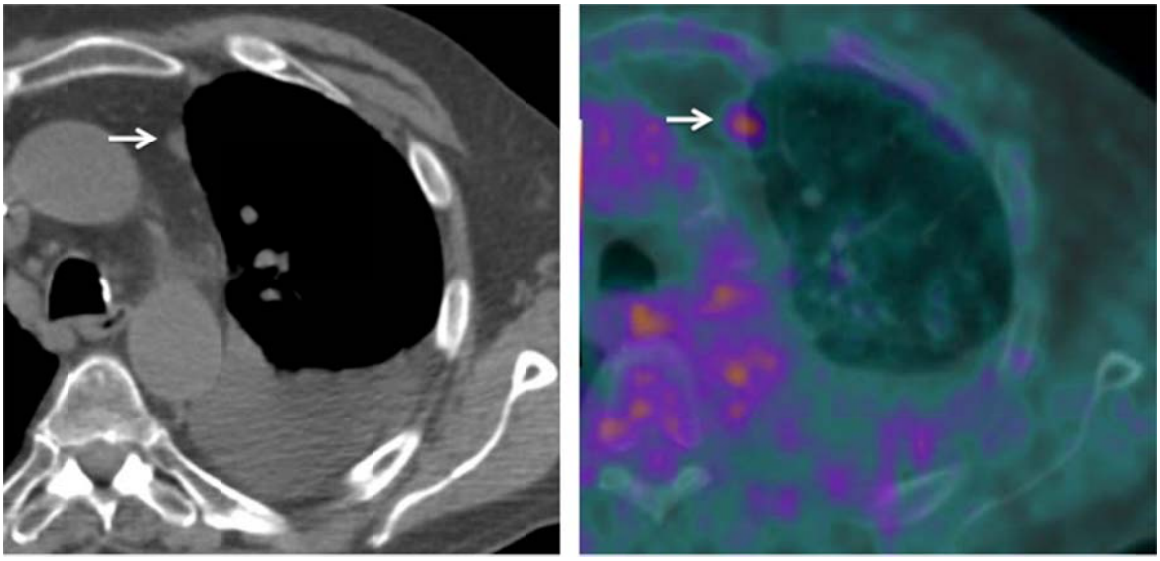

Figure 5: Restaging PET-CT in a 71 year old female with pancreatic adenocarcinoma: (a) Hypermetabolic focus at the right lung base (arrow) without a corresponding nodule on the CT component of the exam (b), represents misregistration of hepatic activity mimicking a lung nodule.

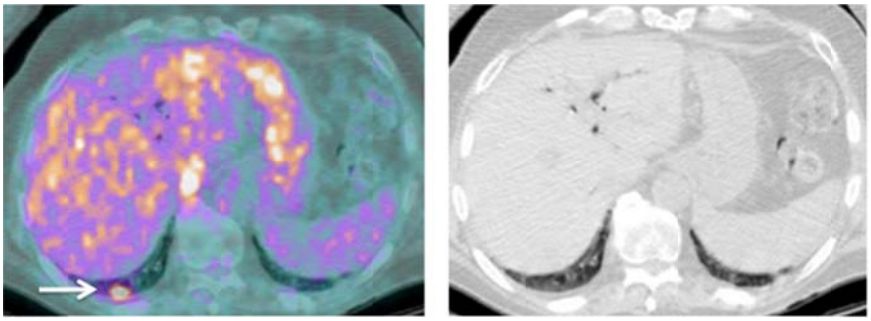

Figure 6: Restaging PET-CT in a 68 year old male status post Whipple's procedure with multiple surgical clips at the surgical site. (a) Dense beam hardening limits evaluation for anatomical details (circle). (b) Fused PET-CT and (c) attenuation-corrected PET demonstrate a hypermetabolic focus (circle) corresponding to the surgical clips. (d) However, no uptake is present on the non-attenuation corrected image, suggesting that this is an attenuation-overcorrection artefact mimicking a lesion.

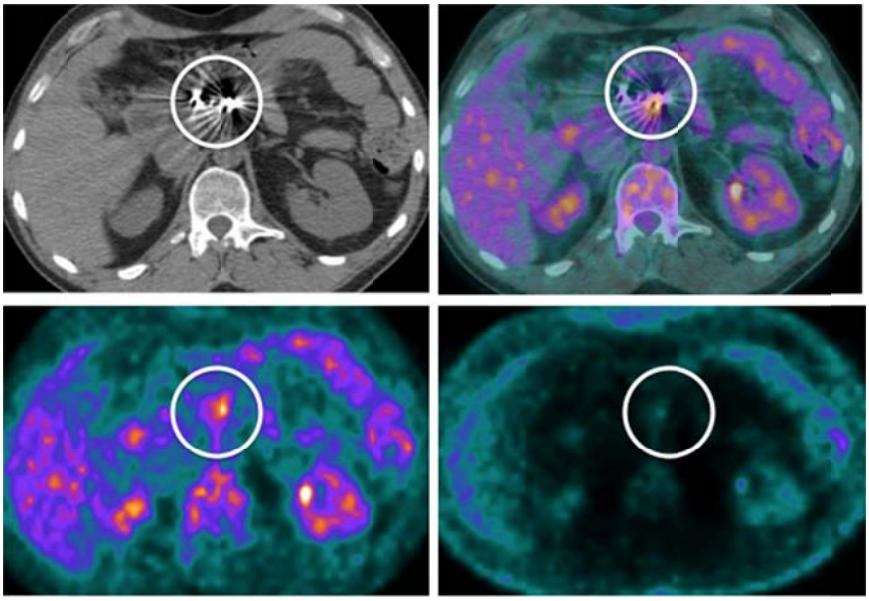

Table 1: Imaging modalities to assess for pancreatic malignancy in the order of preference.

Disease features	**Imaging modalities**
Primary tumor	1. Contrast enhanced CT 2. Contrast enhanced MR imaging 3. PET-CT
Locoregional Spread	1. Contrast enhanced CT 2. PET-CT
Vascular invasion	1. Contrast enhanced CT 2. Contrast enhanced MR imaging
Distant metastases	1. PET-CT 2. Contrast-enhanced CT