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The Role of Positron Emission Tomography in the Management of Pancreatic Cancer

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The role of positron emission tomography (PET) and PET/computed tomography (CT) in the assessment of a patient presenting with cancer of the pancreas is discussed in the overall context of the management of this condition. The clinical limitations persist, with many patients presenting late with unresectable disease and poor prospects for novel drug therapies. PET and PET/CT are best at diagnosing and staging but are relatively inefficient in the detection of nodal disease. The detection of late disease manifestations such as metastatic spread is often of little clinical consequence. PET/CT may be considered as a first-line imaging investigation but evidence for this approach needs to accrue. Overall detection sensitivity at diagnosis varies between 90% and 95% and specificity from 82% to 100%, whereas for staging, sensitivity data vary from 61% to 100% and specificity data from 67% to 100%.
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More than 90% of pancreatic tumors are ductal adenocarcinomas, and another 2% to 5% constitute neuroendocrine and acinar tumors. Worldwide, pancreatic carcinoma ranks 13th in incidence. In the United States, it is the 5th most-common cause of cancer death. It is more common in men and appears to be linked with western diet. Alcohol and smoking also have been identified as significant risk factors.[1,2]

Surgery remains the only potential for long-term survival. However, less than 20% of the patients are candidates for a curative resection because most present with advanced disease.[3] At present, techniques to detect early disease are not yet available. Therefore, accurate diagnosis and staging represent the main determinants of appropriateness and success of treatment. Despite the introduction of more aggressive treatment regimes, long-term survival figures for pancreatic cancer have remained poor, with median survival of 13 to 15 months in patients with localized disease and 3 to 6 months with metastatic disease.

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Clinical Features

Symptoms of pancreatic malignancy often are nonspecific and tend to be ignored by both patient and doctor. Consequently, patients usually present with late-stage disease. Painless jaundice with an associated weight loss is the principal clinical feature that prompts further investigation. In more than 80% of patients, abdominal pain is a late presenting symptom, which is commonly epigastric and diffuse.[4]

Physical signs of pancreatic cancer include abdominal mass, palpable gall bladder (Courvosier's sign), supraclavicular lymphadenopathy (Verchow's node), splenomegaly (caused by portal or splenic vein obstruction), ascites and peripheral edema (caused by portal vein obstruction) These signs usually are associated with advanced disease.[5]

Routine Diagnosis and Staging of Pancreatic Cancer

Basic Investigations

Hematological and Biochemical Parameters

Laboratory findings in pancreatic cancer are nonspecific. Anemia and hypoalbuminemia represent the chronic nature of the condition, and a global derangement of liver enzymes commonly is observed with obstructive jaundice. Malabsorbtion of fat-soluble vitamins because of prolonged biliary obstruction also results in abnormalities of vitamin K-dependent clotting factors. Pancreatic duct obstruction may result

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in pancreatic atrophy and subsequent impaired glucose tolerance or frank diabetes in as many as 70% of patients.[6]

Carbohydrate antigen 19-9 (CA 19-9) is the most commonly used serological marker in pancreatic cancer. Although it has a sensitivity of approximately 80% for detecting pancreatic cancer, it lacks specificity (60-70%) as a result of the levels being increased in a number of other benign and malignant gastrointestinal conditions. As a result, it is not recommended for use as a diagnostic tool but plays an important role in monitoring disease progression and as a prognostic indicator.[7-10]

Conventional Imaging

Ultrasonography

Transabdominal ultrasound (US) is often the first-line investigation in patients presenting with jaundice. It can provide reliable information about the size and site of a tumor, diameter of the biliary tree, and the site of obstruction. It also has been reported to be as accurate as computed tomography (CT) in detecting liver metastases.[11] In addition to these, Doppler ultrasound can be used to interrogate local vessels for tumor infiltration and provide some indication of local resectability.[12] However, US is limited by operator dependence, the patient body habitus, and interposition of gas filled loops of bowel. Consequently, in correctly identifying pancreatic cancer, the accuracy of US has been shown to vary considerably between 57% to 81%.[13]

Recently, novel techniques such as echo-enhanced Doppler sonography[14] and coded-phase inversion harmonic ultrasonography have shown promise.[15] With the latter, sensitivity of 95% has been reported in detecting pancreatic tumors of less than 2 cm. These techniques are not yet routinely available and require validation.

CT

The current modality of choice for diagnosis and staging of pancreatic cancer is fine-slice (1-3 mm), contrast-enhanced, dual-phased multidetector CT (MDCT). MDCT provides superior definition compared with US and gives accurate assessment of local infiltration. Fine slice images acquired with MDCT also can be used to perform intricate reconstructions that allow better visualization of subtle changes in vascular anatomy.[16] Limitations of MDCT stem from the fact that morphological parameters are used to define disease. This is challenging when the lesion being assessed is small (<2 cm) or cystic. Similarly, differentiation between a benign and malignant lesion cannot be reliably made.

The current CT criteria for nonresectability include the presence of distance metastases (to the liver, lungs, or the peritoneum), extensive lymphadenopathy (beyond the peripancreatic chain), malignant ascites or pleural effusion, vascular encasement (causing occlusion or alteration in contour/caliber), and less than 50% contiguity between the tumor and major vessels.[16] Using these criteria, CT can reliably demonstrate nonresectability in almost 100% of the cases.[17] However, it can overestimate resectability in as many as 50% who are later found to have inoperable disease at laparotomy.[14]

Magnetic Resonance Imaging (MRI)

Magnetic resonance cholangiopancreatography (MRCP) is able to demonstrate the anatomy of the biliary tree particularly well. It is reported to be as sensitive as endoscopic retrograde cholangiopancreatodudenography (ERCP) in detecting pancreatic cancer and demonstrates the biliary tree better than CT.[18] However, with the advent and success of MDCT, the routine use of MRI has remained debatable.[19]

ERCP

ERCP has superseded percutaneous transhepatic cholangiopgraphy as the modality of choice for imaging the biliary tract because it avoids puncturing the liver (which reduces the risk of biliary leak and hemorrhage) and allows visualization of adjacent structures (eg, stomach, duodenum, and the ampulla). The principal advantage of ERCP over other imaging techniques is that it confers therapeutic as well diagnostic advantage. Brushings/biopsy specimens can be obtained and stent insertion can be performed simultaneously. ERCP allows the accurate delineation of the site of biliary obstruction and aids in excluding obstruction at multiple levels.[20] When used appropriately and in conjunction with fine-needle aspiration biopsies, it may lead to a definite diagnosis, particularly in small lesions of less that 2 cm.[21] The main complication resulting from ERCP is acute pancreatitis, which has a median incidence of 8.7% (range, 1.6-17.7%).[22] Although the condition often has a mild natural history after ERCP, severer forms have been reported.[23]

Endoscopic Ultrasonography (EUS)

This relatively new procedure involves the use of a high-frequency ultrasound that has been modified for use endoscopicaly. By placing the probe into the stomach and duodenum in close proximity to the pancreas, the whole organ can be visualized and biopsies of the appropriate areas obtained under direct visualization. When compared with CT, EUS has been shown to have a superior sensitivity and specificity, particularly in evaluating tumors less than 3 cm in diameter.[24] It accurately determines local vascular invasion and peripancreatic lymph node involvement with similar results to MDCT. With increasing availability and expertise, EUS is likely to have an expanding role in the management of pancreatic cancer.

Positron Emission Tomography (PET)

Anatomical imaging modalities outlined in previous sections, have formed the corner stone of diagnosis and staging of pancreatic cancer. However, many challenges still remain, which include the definitive diagnosis of small tumors and differentiating malignant and benign inflammatory lesions (eg, caused by mass-forming chronic pancreatitis or secondary to posttreatment fibrosis). The emergence of PET technology has therefore set out to address some of these limitations.

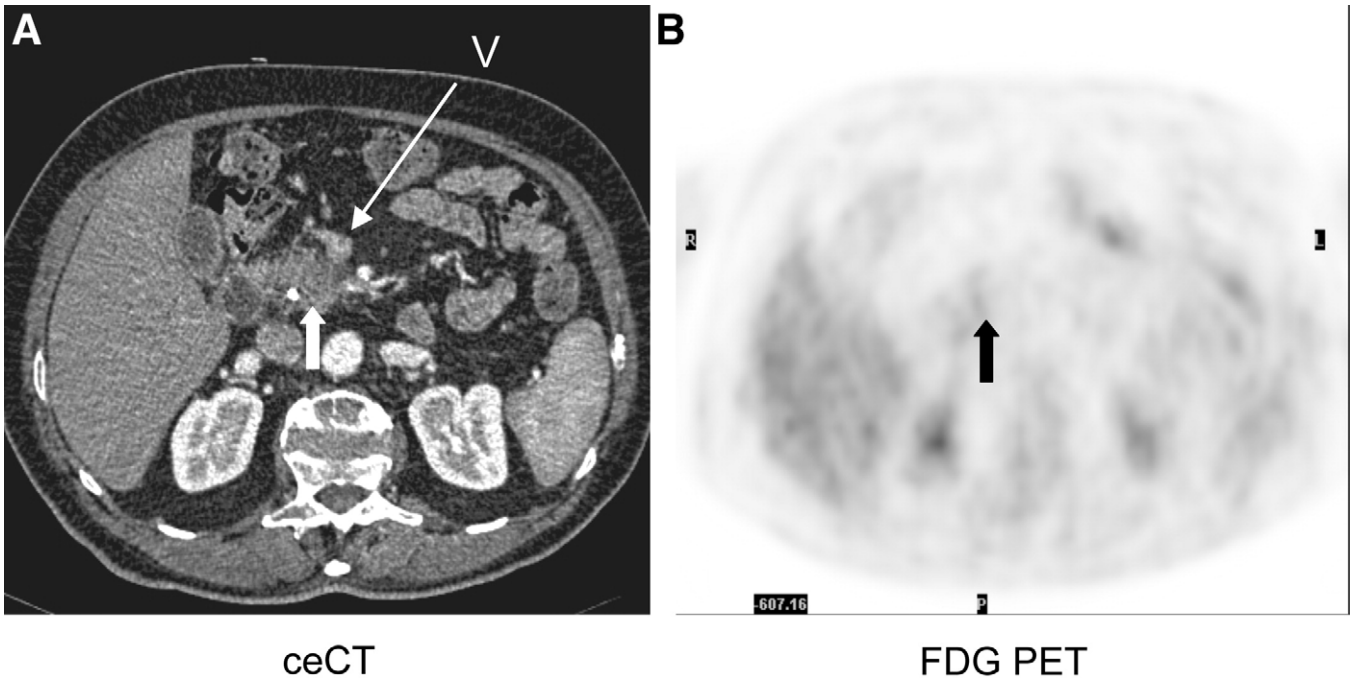

Figure 1 Contrast-enhanced CT scan (A) showing a low density mass in the head of the pancreas (white arrow) and was reported as malignant. The lesion involved the superior mesenteric vein (V) and was deemed inoperable. Conversely, an FDG-PET scan showed no tracer uptake within the pancreas, consistent with a benign pathology. This was confirmed histologically. Here, FDG-PET was able to differentiate between a benign and malignant pathology, where motphological imaging can fail.

The Role of ^{18}F-Fluorodeoxyglucose (FDG)-PET in Diagnosis of Primary Pancreatic Cancer

Much of the present evidence supporting the use of PET in pancreatic cancer has been with the use of the tracer FDG. Because normal pancreas has low glucose utilization, the foci of abnormal FDG uptake can be easily visualized as focal areas of increased activity.[25] Suggestions that FDG would be of value in the diagnosis of malignant pancreatic lesions come from early studies that showed quantitative and selective overexpression of GLUT-1 transporters in pancreatic cancer specimens compared with benign tissue.[26,27] Since then, a number of studies evaluated the clinical role of FDG-PET in primary pancreatic disease. Zimny and coworkers[28] examined the accuracy of FDG-PET in determining the diagnosis in 106 suspicious pancreatic masses. In their series, 70% were histologically confirmed to be adenocarcinoma and 30% to be caused by chronic pancreatitis. Overall, FDG-PET accurately detected 63 of 74 cases with malignancy and 27 of 32 cases of benign disease, giving it an overall sensitivity and specificity of 85% and 84%, respectively.

At initial diagnosis, several studies have shown FDG-PET to be more accurate than conventional imaging techniques. Inokuma and coworkers[29] compared FDG-PET with CT, transabdominal US, and EUS in 35 patients with proven carcinoma. Although FDG-PET correctly identified 33 (94%) patients with cancer, CT, US, and EUS identified 31 (89%), 31 (89%), and 28 (80%), respectively. In another study, which compared FDG-PET with CT and MR, the sensitivity of FDG-PET was found to be lower than CT but better than MR. Its specificity, however, was superior to both (Fig. 1).[30]

A major limitation of morphological imaging techniques is their inability to confidently characterize small as well as cystic lesions. The presence of focal FDG activity irrespective of lesion morphology therefore provides a significant advantage. One study has suggested FDG-PET to be superior to CT in detecting small lesions less than 2 cm in size.[31] Here, PET's sensitivity was shown to be almost 100% compared with 18% for CT. This finding however, was in a relatively small patient group (n = 14) and requires further validation, particularly in the light of recent advances in fine slice CT imaging.

More recently, Sperti and coworkers[32] examined the usefulness of ^{18}F-FDG PET in differentiating malignant from benign pancreatic cysts. In 50 prospectively recruited patients, FDG-PET was more accurate in detecting a malignant cyst (94% for FDG-PET versus 80% for CT). A limitation of this study lay in the fact that it represented a fairly heterogenous and small group of malignant cystic lesions. Therefore, drawing conclusions regarding the diagnostic accuracy of FDG-PET should be done with care. However, the significant finding was that in 31 of 33 (94%) of benign lesions, no FDG uptake was demonstrated and a benign diagnosis was correctly made. The Implications of this, particularly on the management of asymptomatic and high-risk patients are therefore significant.

One of the key strengths of imaging with PET is its quantitative nature, which may be used to bolster its diagnostic

accuracy. Several authors have described tracer semiquantification with standardized uptake values (SUVs) to improve qualitative assessment of PET-detected lesions.[30] Time-dependent changes in tracer uptake have been shown to improve the specificity of FDG-PET. For example, Nakamoto and coworkers[33] demonstrated that at 2 and 3 hours after tracer injection, malignant lesions showed a higher FDG retention index than benign lesions. Combining the tracer retention index with tumor SUV measurements at 2 hours after injection improved the diagnostic accuracy of PET from 83% to 92%. However, this interesting finding was demonstrated in one study of 47 patients and thus requires further investigation. Furthermore, the limitation of any quantitative approach in making the correct diagnosis is in defining a precise cut-off value for tracer uptake. Because benign and malignant lesions in the pancreas can exhibit a wide range of tracer uptake, quantitative image analysis is yet to be proven to be absolute. For this reason, the routine practice of image interpretation with PET, very much leans toward qualitative assessment, where factors such as tracer uptake patterns (ie, focal versus diffuse) can be incorporated.

There is now considerable evidence to support the usefulness of FDG-PET in imaging the pancreas. A tabulated review of published data by Gambhir and coworkers[34] demonstrated that in the 387 patients studied, the weighted average sensitivity and specificity of FDG-PET was 94% and 90%, as compared with 82% and 75% for CT, respectively. Although FDG-PET shows a superior diagnostic yield when compared with conventional imaging with CT, its role in staging the disease and ultimately its impact on management may not be as clear cut.

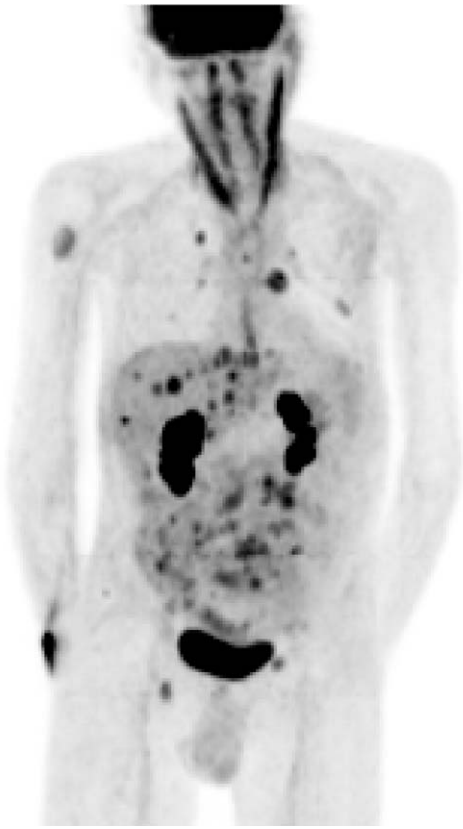

Figure 2 A 48-year-old man presented with weight loss, jaundice and anemia. A contrast-enhanced CT scan of the abdomen showed an unenhancing lesion in the uncinate process, with metastatic deposits only in the liver. The FDG-PET scan clearly demonstrated widespread metastases above and below the diaphragm. The exquisite tumor to background ratio exhibited by FDG-PET allows for accurate whole-body assessment of tumor burden.

Staging Pancreatic Carcinoma With FDG-PET

Local (T) Staging

Poor spatial resolution of FDG-PET limits the local (T) staging of pancreatic cancer. Therefore, anatomical imaging modalities, particularly with MDCT technology and possibly EUS, are better suited to demonstrate the relationship of the tumor, adjacent organs, and vascular structures. At present there are no data to support the usefulness of dual-modality PET/CT in local (T) staging.

Locoregional Lymphnode (N) Staging

In nodal (N) staging of disease, both FDG-PET and CT perform poorly. Reported sensitivities and specificities for FDG-PET have varied between 46% and 71% and 63% and 100% respectively.[35-37] One possible reason for the apparent low sensitivity of FDG-PET is the close proximity of the peripancreatic lymph node basin to the primary tumor, which can obscure their detection.[35,36]

Given the nonspecific nature of FDG, histological confirmation of PET positive lymph nodes is essential, which is particularly important because benign locoregional lymphadenopathy is commonly encountered after biliary instrumentation (eg, ERCP and stent insertion). However, it must be noted that in majority of patients with radiologically inoperable tumors, extensive sampling of positive lymph nodes becomes ethically unfeasible and, consequently, the true accuracy of FDG-PET in detecting lymph nodes metastases often cannot be reported.

Staging of Distant Disease (M Stage)

The major impact of FDG-PET on staging has been in its ability to identify distant metastases (M stage) (Figs. 2 and 3). The liver is the commonest organ to be affected followed by the lungs and the bone marrow. Direct spread into the peritoneum is also not uncommon and often is missed on conventional anatomical imaging. In a series of 89 patients with pancreatic malignancy, Diederichs and coworkers[37] showed the sensitivity and specificity of FDG-PET for detecting hepatic metastases to be 70% and 95%, missing one subcentimeter liver lesion. FDG-PET also detected occult peritoneal metastases in 25% of the cases, once again missing poorly localized and microscopic spread. Similarly, Frohlich and coworkers[38] who looked at the detection of liver metastases with FDG-PET in 168 preoperative patients found FDG-PET to have an overall sensitivity of 68%. In fact, dichotomizing the data into groups with lesions less than or greater than 1 cm showed the sensitivity of PET to be 43% and 97%, respectively. In their series, overall specificity was high (95%), but

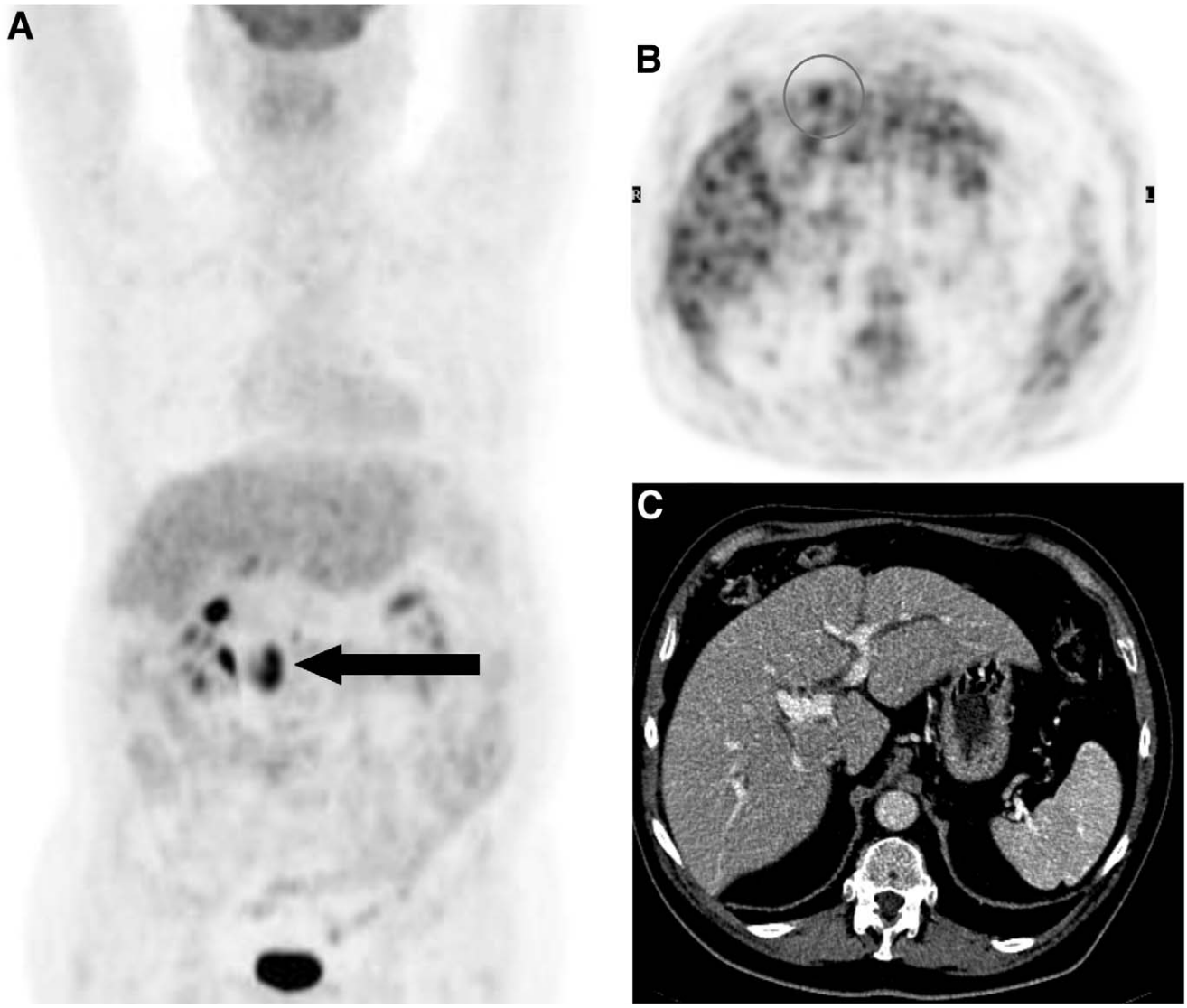

Figure 3 An FDG-PET scan was performed as part of preoperative staging of an operable tumor of the head of the pancreas. The pancreatic lesion can be clearly seen on the MIP image (A; black arrow). The PET axial slice (B) also demonstrates a subcentimeter liver metastases (circle) not previously seen on a staging contrast enhanced CT (C). The patient was therefore treated nonsurgically by chemotherapy.

significant intraheptic cholestasis was a major cause of false positives.

FDG-PET: The Prognostic Significance

There are indications that current methods of tumor staging (TNM) for pancreatic cancer are inadequate. For example, when compared with other more common cancers, node negative pancreatic cancer still caries a poor outcome. This may be attributable to the fact that patients may be understaged histopathologically or that our current clinical and radiological methods are incomplete. As a result, a number of other factors have been assessed as potential predictors of survival in pancreatic cancer, some of which include tumor stage and grade[38,39] R0 resection,[39,40] levels of the tumor marker CA19-9[41] and, more recently, the detection of circulating tumor cells.[42] The ultimate aim is to be able to stratify patients into groups that would most benefit from adjuvant and neoadjuvant treatments.

In addition to the role of PET in staging the disease, the metabolic activity of the tumor may be of prognostic significance. A study of Nakata and coworkers compared the survival of 37 patients with high and low FDG SUVs, using an SUV threshold of 3 (corresponding to the mean FDG SUV level in the series).[43] They found that, although there was no difference in survival between the two SUV groups in patients with respectable disease, in those with inoperable tumors, high SUV correlated with a shorter survival. Multivariate analysis of survival further showed SUV to be an independent prognostic factor in the inoperable group. Sperti and coworkers[44] also demonstrated similar results with in a slightly larger patient series (n = 60). High SUV (>4.0) was again associated with shorter survival, with only 7% (2/29) surviv-

ing beyond 12 months compared with 32% (10/31) with SUV <4.0. Additionally, in the subgroup that were resected, low and high SUV values were associated with mean survival figures of 386 and 224 days, respectively. Multivariate analysis once again revealed that tumor stage and SUV were the only two significant independent predictors of survival when compared with factors such as age, tumors grade, or type of treatment received.

One small study by Maisey and coworkers (n = 11)[45] investigated the role of tumor SUVs in predicting survival from 5-fluorouracil-based chemotherapy. At 1 month after treatment, 6 of 11 patients showed no detectable FDG activity in the tumor and demonstrated better overall survival. Furthermore, in 4 of the 6 responders a correlation with symptomatic improvement was seen.

Measuring proliferation of a tumor is also another potential prognostic indicator. Currently, immunohistochemistry for Ki-67 antigen expression is the method of choice for quantifying proliferation in tissue specimens. The data correlating proliferative activity with FDG have been controversial. Okada and coworkers[46] found a positive correlation between proliferation and FDG uptake in lymphoma cases. Conversely, studies by Francis and coworkers[47]in colorectal cancer and that by Buck and coworkers[48] in pancreatic cancer failed to show a relationship. There may be a potential for alternative tracers such as ^{11}C-thymidine or the thymidine analog 3′-deoxy-3′-[18F]-fluorothymidine (^{18}F-FLT) in prognosticating pancreatic cancer but, at present, no published series are available.

FDG-PET in the Detection of Recurrent Pancreatic Cancer

Serial measures of tumor marker levels (CA 19-9) are a sensitive indicator of disease recurrence. However, differentiating recurrent disease from postsurgical/radiotherapy changes with CT or MRI is difficult. Molecular imaging, on the other hand, can detect focal tracer accumulation regardless of morphology. To date, few studies have examined the use of FDG-PET in detecting disease recurrence. Rose and coworkers[31] looked at eight patients with increasing tumor marker levels or indeterminate CT findings. FDG-PET correctly identified recurrent disease in all, with four occurring in the surgical bed and four as new liver metastases. More recently, Ruf and coworkers showed that in 31 patients with suspected recurrent disease, 96% of local recurrences were detected with FDG as compared with 23% with CT or MRI.[49] In detecting metastatic disease in the liver, CT-MRI was more sensitive, particularly in identifying small lesions, but FDG-PET additionally helped to detect occult nonregional and extra-abdominal disease.

There are therefore indications that FDG-PET may be useful in differentiating fibrosis from recurrent disease, in whole body restaging of the patient and in identifying the focus of recurrence, where there is an increase in tumor marker levels in the face of a negative or equivocal finding by conventional imaging.

Pitfalls of Imaging Pancreatobiliary Disease With FDG-PET

In imaging pancreatic disease with FDG-PET, serum glucose levels are an important consideration, especially when pancreatic insufficiency and diabetes are commonly found in this cohort of patients. High serum glucose levels are believed to compete with FDG for glucose transporters sites and thus reduce the sensitivity of detecting malignant lesions. In 106 patients with suspected pancreatic carcinoma, Zimny and coworkers[28] found that 10 of 11 false-negative results occurred in hyperglycemic patients, thus resulting in sensitivity of FDG-PET to be 98% in euglycemic as compared with 63% in hyperglycemic patients with a pancreatic tumor.

Lesion size poses a further challenge, where the sensitivity of FDG-PET in detecting subcentimeter lesions can be low. This problem is not exclusive to that of pancreatic pathology and represents the effect of partial volume averaging of the signal from a small lesion. The advent of dual-modality PET/CT, which uses its CT component for density attenuation correction, has partly helped to address this limitation. Furthermore, developments in PET detector technology are continually improving the spatial resolution of PET, which currently stands at between 0.5 and 0.8 cm using the third-generation detector systems.

Several benign clinical conditions also may result in focal FDG accumulation and, thus, false-positive findings. FDG, despite its exquisite sensitivity, is not tumor specific, and uptake by inflammatory tissue often is encountered. Although FDG-PET has been shown to be better than morphological imaging in differentiating benign from malignant lesions, focal accumulation in areas of active pancreatitis can commonly be seen. In the face of elevated C-reactive protein levels, specificity of FDG-PET has been reported to be as low as 50%.[50] It is therefore recommended that C-reactive protein levels are routinely checked before an FDG-PET study. Nonspecific FDG uptake also can seen after biliary instrumentation, hemorrhage into a pancreatic pseudocyst, secondary to portal vein thrombosis and in retroperitoneal fibrosis. This is once again another area that PET/CT fusion is set to impact, where the addition of anatomical data can improve the accuracy and certainty of image interpretation.

Pancreatic Cancer and Image Fusion With PET/CT

Combining the anatomical and biological data are of particular advantage in imaging the abdomen because a number of intraabdominal organs (such as the bowel) exhibit nonspecific FDG uptake. This can result in diagnostic uncertainty and potential false-positive results. In a study of colorectal cancer patients, PET/CT resulted in improvement of lesion localization, certainty of diagnosis, and a subsequent reduction in false-positive findings. The information from the CT component of PET/CT also can provide additional clinically useful information. This has therefore offered a strong rationale for the use of PET/CT as a single investigation of choice in oncology.

To date, only 2 studies have examined the role of PET and

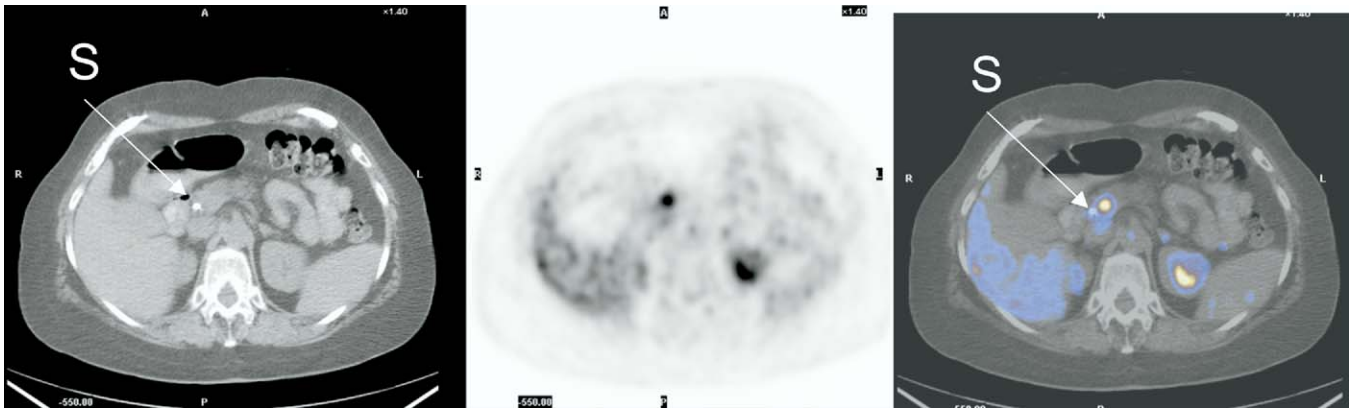

Figure 4 A 70-year-old woman presented with painless obstructive jaundice and negative ultrasound and CT findings. An ERCP suggested a short stricture of the distal common bile duct and a biliary stent was inserted. The FDG PET/CT shown above, demonstrates a lesion in the head of the pancreas, adjacent to the biliary stent (S). Anatomical localization of the PET-positive lesion directed further imaging with EUS and a biopsy, which confirmed the diagnosis of pancreatic adenocarcinoma.

CT image fusion in pancreatic cancer. Lemke and coworkers[51] showed that retrospective fusion of CT and FDG-PET images resulted in an improvement in the sensitivity of both imaging modalities (CT: 76.%; PET: 84.4%; fused: 89.1%). The sensitivity of detecting infiltration of adjacent tissues by the cancer also improved over that of CT alone; however, it occurred at the expense of a reduced specificity. This is a particularly undesirable situation because overstaging the disease can deny a patient a potentially curative resection. Finally, image fusion also resulted in a slight (but statistically insignificant) improvement in sensitivity for detecting lymph node metastases (PET = 25.8%; CT = 25.8%; fused = 32.3%), but the specificities remained unchanged (75%).

More recently, Heinrich and coworkers[52] investigated the role and cost-effectiveness of imaging with an integrated PET/CT scan on the management of 59 patients with a potentially resectable pancreatic tumor. The important point of note in this study was that PET/CT was acquired with a low dose, unenhanced CT scan according to current routine protocols. Overall, the accuracy of FDG-PET/CT for detecting pancreatic cancer was similar to that of previous studies that used PET alone. In 5 patients (16%), detection of CT occult metastases by FDG-PET/CT resulted in avoidance of surgery and thus significant cost saving. In fact PET-CT was shown to be cost effective despite patients requiring other investigations (eg, EUS/CT-guided biopsies, staging laparoscopy) to confirm the nature of PET detected lesions. Although the indications are that FDG-PET/CT may be useful in the routine management of pancreatic cancer, future large studies are still awaited.

The Impact of FDG-PET on the Management of Pancreatic Cancer

The major challenge of managing pancreatic cancer is its late presentation. Currently there are no established screening programs that would identify the disease early and at present, there is no justification for using FDG-PET as a population-wide screening tool (Fig. 4). Although a number of aforementioned studies suggest FDG-PET to be of value in earlier diagnosis of pancreatic cancer, these need to be interpreted within context of the natural history of the disease. In majority of cases, initiation of investigations occurs after the development of clinical signs and symptoms that may indicate advanced disease. Therefore, by the time the patient undergoes some form of imaging, there is an 80% chance that the disease has become unresectable. It therefore becomes clear that at present, the true impact of FDG-PET or PET/CT on the management of pancreatic cancer occurs at initial diagnosis and staging and not earlier.

Using FDG-PET, the detection sensitivity at diagnosis can vary between 90% and 95% and its specificity from 82% to 100%. In staging, sensitivities and specificities also range between 61% and 100% and 67% and 100%. Consequently, this variation can result in a change in management effect of between 36% and 50%. The strength of biological imaging lies in its ability to detect pathology, irrespective of lesion morphology; a property that inherently gives FDG-PET its strength in detecting small or cystic lesions and in differentiating benign from malignant disease. In this setting, FDG-PET can alter management by providing a more accurate diagnosis.

The evidence so far suggests that both PET and CT are poor at nodal staging of disease. In detecting metastatic disease, the impact of FDG-PET on management is also not clear. The limitations are the fact that our management of pancreatic cancer has changed little over the years. Surgery continues to be the only treatment that offers potential cure. Therefore, defining whether the patient has an operable tumor remains the ultimate aim of imaging in pancreatic cancer. In this setting CT and EUS may be best suited, as the lack of anatomical definition and poor spatial resolution of PET, limit local staging of disease. Subsequently, the detection of occult or additional metastases with PET may not be relevant if the patient has in any case an inoperable tumor. Although this may argue against the routine use of FDG-PET in the management of pancreatic cancer, we believe that it actually provides a strong argument for a “one-stop-shop” approach

to imaging with PET/CT. However, to achieve the full potential of this approach, the CT component of PET/CT needs to be performed at maximum settings to provide full diagnostic information. Future work is therefore required to determine the effects of contrast material and high power CT on the attenuation correction of FDG-PET images. The feasibility and cost implications of this approach for routine clinical use will also need to be determined.

References

1. Gold EB, Goldin SB: Epidemiology of and risk factors for pancreatic cancer. Surg Oncol Clin N Am 7:67-91, 1998
2. Heuch I, Kvale G, Jacobsen BK, et al: Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer 48:637-643, 1983
3. Li D, Xie K, Wolff R, Abbruzzese JL: Pancreatic cancer. Lancet 27; 363(9414):1049-1057, 2004
4. DiMagno EP: Pancreatic cancer: clinical presentation, pitfalls and early clues. Ann Oncol 10:140-142, 1999 (suppl 4)
5. Takhar AS, Palaniappan P, Dhingsa R, et al: Recent developments in diagnosis of pancreatic cancer. BMJ 18; 329:668-673, 2004
6. Saruc M, Pour PM: Diabetes and its relationship to pancreatic carcinoma. Pancreas 26:381-387, 2003
7. Bluemke DA, Abrams RA, Yeo CJ, et al: Recurrent pancreatic adenocarcinoma: spiral CT evaluation following the Whipple procedure. Radiographics 17:303-313, 1997
8. Ozkan H, Kaya M, Cengiz A: Comparison of tumor marker CA 242 with CA 19-9 and carcinoembryonic antigen (CEA) in pancreatic cancer. Hepatogastroenterology 50:1669-1674, 2003
9. Willett CG, Daly WJ, Warshaw AL: CA 19-9 is an index of response to neoadjunctive chemoradiation therapy in pancreatic cancer. Am J Surg 172:350-352, 1996
10. Yeo TP, Hruban RH, Leach SD, et al: Pancreatic cancer. Curr Probl Cancer 26:176-275, 2002
11. Minniti S, Bruno C, Biasiutti C, et al: Sonography versus helical CT in identification and staging of pancreatic ductal adenocarcinoma. J Clin Ultrasound 31:175-182, 2003
12. Clarke DL, Thomson SR, Madiba TE, et al: Preoperative imaging of pancreatic cancer: a management-oriented approach. J Am Coll Surg 196:119-129, 2003
13. Haycox A, Lombard M, Neoptolemos J, et al: Review article: current practice and future perspectives in detection and diagnosis of pancreatic cancer. Aliment Pharmacol Ther 12:937-948, 1998
14. Rickes S, Unkrodt K, Neye H, et al: Differentiation of pancreatic tumours by conventional ultrasound, unenhanced and echo-enhanced power Doppler sonography. Scand J Gastroenterol 11:1313-1320, 2002
15. Kitano M, Kudo M, Maekawa K, et al: Dynamic imaging of pancreatic diseases by contrast enhanced coded phase inversion harmonic ultrasonography. Gut 53:854-859, 2004
16. Smith SL, Rajan PS: Imaging of pancreatic adenocarcinoma with emphasis on multidetector CT. Clin Radiol 59:26-38, 2004
17. Fuhrman GM, Charnsangavej C, Abbruzzese JL, et al:. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. Am J Surg 167:104-111; discussion 111-103, 1994
18. Adamek HE, Albert J, Breer H, et al: Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. Lancet 15; 356:190-193, 2000
19. Hanbidge AE: Cancer of the pancreas: the best image for early detection—CT, MRI, PET or US? Can J Gastroenterol 16:101-105, 2002
20. Conio M, Demarquay JF, De Luca L, et al: Endoscopic treatment of pancreatico-biliary malignancies. Crit Rev Oncol Hematol 37:127-135, 2001
21. Graham RA, Bankoff M, Hediger R, et al: Fine-needle aspiration biopsy of pancreatic ductal adenocarcinoma: loss of diagnostic accuracy with small tumors. J Surg Oncol 55:92-94, 1994
22. Mariani A: Pharmacological prevention of post-ERCP pancreatitis: which therapy is best? JOP 4:68-74, 2003
23. Fung AS, Tsiotos GG, Sarr MG: ERCP-induced acute necrotizing pancreatitis: is it a more severe disease? Pancreas 15:217-221, 1997
24. Mertz HR, Sechopoulos P, Delbeke D, et al: EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma. Gastrointest Endosc 52: 367-371, 2000
25. Berberat P, Friess H, Kashiwagi M, et al: Diagnosis and staging of pancreatic cancer by positron emission tomography. World J Surg 23: 882-887, 1999
26. Higashi T, Tamaki N, Honda T, et al: Expression of glucose transporters in human pancreatic tumors compared with increased FDG accumulation in PET study. J Nucl Med 38:1337-1344, 1997
27. Reske SN, Grillenberger KG, Glatting G, et al: Overexpression of glucose transporter 1 and increased FDG uptake in pancreatic carcinoma. J Nucl Med 38:1344-1348, 1997
28. Zimny M, Bares R, Fass J, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography in the differential diagnosis of pancreatic carcinoma: a report of 106 cases. Eur J Nucl Med 24:678-682, 1997
29. Inokuma T, Tamaki N, Torizuka T, et al: Evaluation of pancreatic tumors with positron emission tomography and F-18 fluorodeoxyglucose: comparison with CT and US. Radiology 195:345-352, 1995
30. Koyama K, Okamura T, Kawabe J, et al: Diagnostic usefulness of FDG PET for pancreatic mass lesions. Ann Nucl Med 15:217-224, 2001
31. Rose DM, Delbeke D, Beauchamp RD, et al: 18Fluorodeoxyglucose-positron emission tomography in the management of patients with suspected pancreatic cancer. Ann Surg 229:729-737; discussion 737-728, 1999
32. Sperti C, Pasquali C, Decet G, et al: F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. J Gastrointest Surg 9:22-28; discussion 28-29, 2005
33. Nakamoto Y, Higashi T, Sakahara H, et al: Delayed (18)F-fluoro-2-deoxy-D-glucose positron emission tomography scan for differentiation between malignant and benign lesions in the pancreas. Cancer 89:2547-2554, 2000
34. Gambhir SS, Czernin J, Schwimmer J, et al: A tabulated summary of the FDG PET literature. J Nucl Med 42:1S-93S, 2001 (suppl 5)
35. Bares R, Dohmen BM, Cremerius U, et al: [Results of positron emission tomography with fluorine-18 labeled fluorodeoxyglucose in differential diagnosis and staging of pancreatic carcinoma]. Radiologe 36:435-440, 1996
36. Bares R, Klever P, Hauptmann S, et al: F-18 fluorodeoxyglucose PET in vivo evaluation of pancreatic glucose metabolism for detection of pancreatic cancer. Radiology 192:79-86, 1994
37. Diederichs CG, Staib L, Vogel J, et al: Values and limitations of 18F-fluorodeoxyglucose-positron-emission tomography with preoperative evaluation of patients with pancreatic masses. Pancreas 20:109-116, 2000
38. Frohlich A, Diederichs CG, Staib L, et al: Detection of liver metastases from pancreatic cancer using FDG PET. J Nucl Med 40:250-255, 1999
39. Lim JE, Chien MW, Earle CC: Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 237:74-85, 2003
40. Wittekind C, Compton CC, Greene FL, et al: TNM residual tumor classification revisited. Cancer 94:2511-2516, 2002
41. Sperti C, Pasquali C, Catalini S, et al: CA 19-9 as a prognostic index after resection for pancreatic cancer. J Surg Oncol 52:137-141, 1993
42. Vogel I, Kalthoff H, Henne-Bruns D, et al: Detection and prognostic impact of disseminated tumor cells in pancreatic carcinoma. Pancreatology 2:79-88, 2002
43. Nakata B, Nishimura S, Ishikawa T, et al: Prognostic predictive value of 18F-fluorodeoxyglucose positron emission tomography for patients with pancreatic cancer. Int J Oncol 19:53-58, 2001
44. Sperti C, Pasquali C, Chierichetti F, et al: 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. J Gastrointest Surg 7:953-959; discussion 959-960, 2003
45. Maisey NR, Webb A, Flux GD, et al: FDG-PET in the prediction of

survival of patients with cancer of the pancreas: a pilot study. Br J Cancer 83:287-293, 2000
46. Okada J, Yoshikawa K, Itami M, et al: Positron emission tomography using fluorine-18-fluorodeoxyglucose in malignant lymphoma: a comparison with proliferative activity. J Nucl Med 33:325-329, 1992
47. Francis DL, Freeman A, Visvikis D, et al: In vivo imaging of cellular proliferation in colorectal cancer using positron emission tomography. Gut 11:1602-1606, 2003
48. Buck AC, Schirrmeister HH, Guhlmann CA, et al: Ki-67 immunostaining in pancreatic cancer and chronic active pancreatitis: does in vivo FDG uptake correlate with proliferative activity? J Nucl Med 42:721-725, 2001
49. Ruf J, Lopez Hanninen E, Oettle H, et al: Detection of recurrent pancreatic cancer: comparison of FDG-PET with CT/MRI. Pancreatology 5:266-272, 2005.
50. Shreve PD: Focal fluorine-18 fluorodeoxyglucose accumulation in inflammatory pancreatic disease. Eur J Nucl Med 25:259-264, 1998
51. Lemke AJ, Niehues SM, Hosten N, et al: Retrospective digital image fusion of multidetector CT and 18F-FDG PET: clinical value in pancreatic lesions–a prospective study with 104 patients. J Nucl Med 45: 1279-1286, 2004
52. Heinrich S, Goerres GW, Schafer M, et al: Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg 242:235-243, 2005