PET and PET-CT for Evaluation of Colorectal Carcinoma

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The evaluation of patients with known or suspected recurrent colorectal carcinoma is now an accepted indication for positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) imaging. FDG-PET does not replace imaging modalities such as computed tomography (CT) for preoperative anatomic evaluation but is indicated as the initial test for diagnosis and staging of recurrence and for preoperative staging (N and M) of known recurrence that is considered to be resectable. FDG-PET imaging is valuable for the differentiation of posttreatment changes from recurrent tumor, differentiation of benign from malignant lesions (indeterminate lymph nodes, hepatic and pulmonary lesions), and the evaluation of patients with rising tumor markers in the absence of a known source. The addition of FDG-PET to the evaluation of these patients reduces overall treatment costs by accurately identifying patients who will and will not benefit from surgical procedures. Although initial staging at the time of diagnosis is often performed during colectomy, FDG-PET imaging is recommended for a subgroup of patients at high risk (with elevated CEA levels) and normal CT and for whom surgery can be avoided if FDG-PET shows metastases. Screening for recurrence in patients at high risk has also been advocated. FDG-PET imaging seems promising for monitoring patient response to therapy but larger studies are necessary. The diagnostic implications of integrated PET-CT imaging include improved detection of lesions on both the CT and FDG-PET images, better differentiation of physiologic from pathologic foci of metabolism, and better localization of the pathologic foci. This new powerful technology provides more accurate interpretation of both CT and FDG-PET images and therefore more optimal patient care. PET-CT fusion images affect the clinical management by guiding further procedures (biopsy, surgery, radiation therapy), excluding the need for additional procedures, and changing both inter- and intramodality therapy.

THE RAPID ADVANCES in imaging technologies are a challenge for physicians who must integrate these technologies for optimal patient care and outcomes at minimal cost. Since the early 1990s, numerous technological improvements have occurred in the field of radiological imaging. These include 1) multislice spiral computed tomography (CT), which permits the fast acquisition of CT angiographic images and multiphase enhancement techniques, and 2) positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) as a radiopharmaceutical that provides the capability for imaging glucose metabolism. Multiple indications for molecular imaging using FDG are now well accepted in the fields of neurology, cardiology, and oncology.[1]

The goals of oncologic imaging are lesion detection, lesion characterization, evaluation of the extent of the neoplasm, staging for malignant lesions, and assessment of the therapeutic response. Staging includes lesion localization, evaluation of proximity to vessels, and detection of nodal and distant metastases. Some of these goals are better achieved with the high resolution of anatomical imaging techniques and others with molecular imaging using PET.

Molecular imaging using positron imaging is unique in that positron emitters allow labeling of radiopharmaceuticals that closely mimic endogenous molecules, and there are continuing efforts to development of new biological tracers. FDG because of its relatively long half life and its ability to assess cellular glucose metabolism is the radiopharmaceutical most widely used with the PET technology; it has been approved by the Center for Medical Services for reimbursement by Medicare in the evaluation of patients with extracranial neoplasms, myocardial viability and in the presurgical assessment of intractable epilepsy.

A wide variety of malignant tumors avidly accumulate FDG. This is the result of increased numbers of glucose transporter proteins and increased intracellular enzyme levels of hexokinase and phosphofructokinase, among others, which promote glycolysis.[2-5] FDG-PET imaging can be used to exploit the metabolic differences between benign and malignant cells for imaging purposes.[6,7] The widespread oncologic applications including differentiation of benign from malignant lesions, staging malignant lesions, detection of malignant recurrence, and monitoring therapy have contributed to the establishment of the PET technology in many medical centers in the United States, Europe, and progressively throughout the world. Improvements in the distribution of FDG by commercial companies have now made FDG available to many medical centers as well.

Although numerous studies have shown that the sensitivity and specificity of FDG imaging is superior to that of CT in many clinical settings, the inability of FDG imaging to provide anatomical localization remains a

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significant impairment in maximizing its clinical value. Because FDG is a tracer of glucose metabolism, its distribution is not limited to malignant tissue. To avoid errors, the interpreter must be familiar with the normal pattern and physiologic variations of FDG distribution and with clinical data relevant to the patients.[8,9] It is also important to standardize the environment of the patient during the uptake period so as to limit physiologic variations of FDG uptake, (eg, in activated muscular tissue). The problem of precise anatomical localization of the foci of abnormal uptake and differentiation of physiologic from pathologic uptake is compounded by the lower resolution and increased noise in the images of many of the systems at the low end of the spectrum and especially the hybrid gamma camera-based systems.

Limitations of anatomical imaging with CT are well-known and are related to 1) size criteria for differentiating benign from malignant lymph nodes, 2) difficulty differentiating posttherapy changes from tumor recurrence, and 3) difficulty differentiating nonopacified loops of bowel from metastases in the abdomen and pelvis.

Close correlation of FDG studies with conventional CT scans helps to minimize these difficulties. In practice for the past ten years, interpretation has been accomplished by visually comparing corresponding FDG and CT images. The interpreting physician visually integrates the two image sets to precisely locate a region of increased uptake on the CT scan. To aid in image interpretation, computer software has been developed to coregister the FDG-PET emission scans with the high-resolution anatomical maps provided by CT.[10] Another approach that has gained wider acceptance recently is the hardware approach to image fusion using multimodality imaging with an integrated PET-CT imaging system.[11] The recent technical development of integrated PET-CT systems provides CT and FDG-PET images obtained in a single imaging setting allowing optimal coregistration of images. The fusion images provided by these systems allow accurate interpretation of both CT and FDG-PET studies.

These advances in imaging technologies bring another challenge to physicians at times when it is also important to provide care at an acceptable cost. Increasing cost-effectiveness and decreasing the number of invasive procedures are currently two of the major trends in health care. Pursuant to these goals, considerable attention has recently been directed toward the use of metabolic imaging using FDG-PET in the evaluation of patients with cancer. Metabolic imaging, used in the appropriate setting, allows significant reduction in the utilization of more costly and invasive surgical methods for diagnosing and staging disease in patients with suspicious lesions.

Normal Distribution of FDG

To interpret FDG images, one must be familiar with the normal distribution of FDG, physiological variations, and benign conditions that accumulate FDG.[8,9,12] Some physiological variations are important for interpretation of FDG in colorectal carcinoma. Uptake in the gastrointestinal tract is variable from patient to patient and uptake along the esophagus is common, especially in the distal portion and at the gastroesophageal junction and in the presence of esophagitis; the esophagus is best identified on sagittal views. The wall of the stomach is usually faintly seen and can be used as an anatomical landmark, but occasionally the uptake can be relatively intense. There is uptake in the cecum of many patients that may be related to abundant lymphoid tissue in the intestinal wall, among other factors. When marked activity is present in the bowel, evaluation for recurrence at the anastomotic site can be difficult. Mild-to-moderate uptake is also usually seen at colostomy sites.

Unlike glucose, FDG is filtered by the glomerulus and excreted into the urine. The accumulation of FDG in the renal collecting system may mask FDG uptake in adjacent organs. Therefore, the patient should be kept well hydrated to promote diuresis. For optimal evaluation of the pelvis, the bladder should be empty. Therefore, patients are usually asked to void before acquisition of the images and images are acquired from the pelvis to the cranium. The administration of furosemide can occasionally be useful to avoid focal ureteral activity.

In the resting state, there is low accumulation of FDG in the muscular system, but following exercise significant accumulation of FDG occurs in selected muscular groups, and may mislead the interpreter. Hyperventilation may induce uptake in the diaphragm and stress-induced muscle tension is often seen in the trapezius and paraspinal muscles. Muscle relaxants such as benzodiazepines (diazepam, 5-10 mg orally, 30-60 min before FDG administration) may be helpful in these tense patients. The PET-CT technology allowed characterization of FDG uptake in metabolically active fatty tissue (brown fat) that was previously believed to be muscle uptake.[13] In patients with lung tumors and laryngeal nerve palsy, PET-CT images helped to localize unilateral FDG uptake at the base of the neck in the contralateral vocal cord,[14] allowing discrimination between physiological laryngeal uptake from metastasis or a second primary neoplasm.

Inflammation in general can result in FDG uptake that can be severe enough to be confused with malignant lesions, especially when there is granulomatous inflammation, including tuberculosis, sarcoidosis, histoplasmosis and aspergillosis among others.[15] This is particularly important when evaluating patients posttreatment; for example, sites of surgical intervention demonstrate FDG uptake in the early healing phase due to inflammatory

changes. Inflammatory changes after radiation therapy can make interpretation of FDG uptake challenging as well, although comparison with baseline FDG images and knowledge of the radiation port are helpful. Postradiation therapy uptake may persist for several months.

It is critical to standardize the environment of the patient during the uptake period to examine the patient for postoperative sites, tube placement, stoma, etc., and to know the history and time of invasive procedure and therapeutic interventions to avoid misinterpretation of FDG images. In addition, a 4-h fasting period is recommended including no consumption of beverages with sugar and no intravenous dextrose; a 12-h fasting period is better if the chest is evaluated to prevent myocardial uptake. Drinking water should be encouraged to keep the patient hydrated and promote diuresis, which will decrease activity in the renal collecting system and the bladder. Patients are advised to avoid strenuous exercise for the preceding 24 h.

DIAGNOSIS AND INITIAL STAGING OF COLORECTAL CANCER

Colorectal cancer is the third most common cause of cancer in men and women and affects 5% of the population in the United States and most western countries. The American Cancer Society estimates that there are approximately 135,000 new cases of colorectal cancer per year in the United States and approximately 57,000 patients per year die from this disease in the United States, representing 10% of all cancer deaths. Approximately 70-80% of patients are treated with curative intent and the overall survival at 5 years is less than 60%. The diagnosis of colorectal carcinoma is based on colonoscopy and biopsy. The preoperative staging with imaging modalities is usually limited because most patients will benefit from colectomy to prevent intestinal obstruction. The extent of the disease can be evaluated during surgery.

Three studies have been performed to evaluate the performance of FDG-PET in the initial staging of colorectal cancer. Abdel-Nabi and coworkers[16] evaluated the usefulness of FDG-PET for staging patients with known or suspected primary colorectal carcinomas. In 48 patients, FDG-PET imaging identified all primary carcinomas. They found that FDG and CT were equally poorly sensitive for detecting local lymph node involvement, both with a sensitivity of 29%. FDG-PET was, however, superior to CT for detecting hepatic metastases, with sensitivity and specificity of 88% and 100% respectively compared with 38% and 97% for CT. These data were confirmed in the studies of Mukai and coworkers[17] and Kantorova and coworkers,[18] which also reported that FDG-PET changed the treatment modality in 8% of patients and the range of surgery in 13%. False-positive findings include abscesses, fistulas, diverticulitis and occasionally adenomas. Figure 1 illustrates the example of a patient presenting with multiple hepatic lesions on CT, a biopsy revealed adenocarcinoma and no primary was found. FDG-PET-CT imaging identified the primary colon carcinoma (the color version of this figure is available online).

In addition, a study of 110 patients has demonstrated that these precancerous adenomatous polyps can be detected incidentally on whole body images performed for other indications with a sensitivity of 24% (24/59). The size of the lesions ranged from 5 to 30 mm. The positivity rate increased to 90% for lesions greater than 13 mm in size, and the false-positive rate was 5.5% (6/10).[19] Although PET is not recommended for detection or screening for precancerous or malignant colonic neoplasms, the identification of focal colon uptake should not be ignored.

Although the sensitivity of FDG-PET for the detection of a primary colon carcinoma may be high, its role in the preoperative staging is still debated except in high-risk patients for whom surgery can be avoided if metastases are identified.

DETECTION OF RECURRENT OR METASTATIC COLORECTAL CARCINOMA

Approximately 70% of the patients are resectable with curative intent but recurrence is noted in one third of these patients in the first 2 years after resection. Twenty-five percent of these patients have recurrence limited to one site and are potentially curable by surgical resection.[20] For example, about 14,000 patients per year present with isolated liver metastases as their first recurrence, and about 20% of these patients die with metastases exclusively to the liver.[21] Hepatic resection is the only curative therapy in these patients, but it is associated with a mortality of 2 to 7% and has the potential for significant morbidity.[22] Early detection and prompt treatment of recurrences may lead to a cure in up to 25% of patients. However, the size and number of hepatic metastases and the presence of extra-hepatic disease affect the prognosis. The poor prognosis of extra-hepatic metastases is believed to be a contraindication to hepatic resection.[23] Therefore, accurate noninvasive detection of inoperable disease with imaging modalities plays a pivotal role in selecting patients who would benefit from surgery.

Conventional Modalities for Detecting and Staging Recurrence

The measurement of serum levels of carcinoembryonic antigen may be used to monitor the detection of recurrence with a sensitivity of 59% and specificity of 84% but does not localize recurrent lesions.[24] Barium studies have been used for detection of local recurrence with accuracy in the range of 80%. However, barium

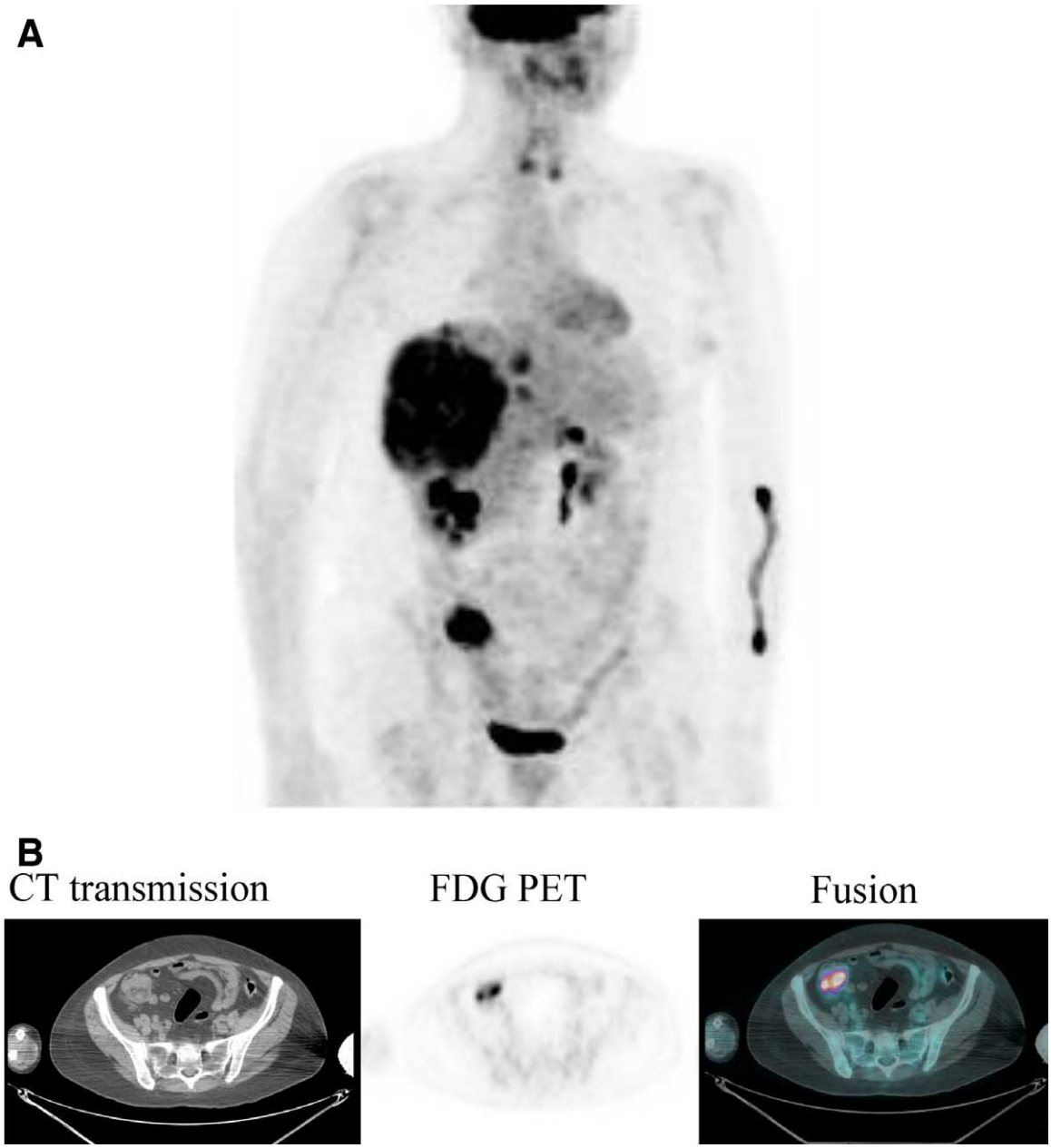

Fig 1. A 45-year-old female with multiple hepatic lesions was found to have adenocarcinoma at biopsy. The conventional workup failed to demonstrate a primary tumor. Whole-body positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) imaging was performed using an integrated PET-computed tomography (CT) imaging system providing transmission CT images, FDG-PET images, and fusion images. A, FDG-PET maximum intensity projection (MIP) image demonstrates: 1) multiple lesions in the liver that are FDG-avid and 2) a focus of uptake in the right upper pelvis. B, A PET-CT transaxial view through the right upper pelvis demonstrates that the focus of uptake corresponds to a lesion in the wall of the cecum suggesting a primary colon carcinoma. A repeat colonoscopy revealed colon carcinoma.

studies have been reported to be only 49% sensitive and 85% specific for overall recurrence.[25]

CT has been the conventional imaging modality used to localize recurrence with an accuracy of 25 to 73%, but it fails to demonstrate hepatic metastases in up to 7% of patients and underestimates the number of lobes involved in up to 33% of patients. In addition, metastases to the peritoneum, mesentery and lymph nodes are commonly missed on CT, and the differentiation of postsurgical changes from local tumor recurrence is often equivo-

cal.[26-30] Among the patients with negative CT, 50% will be found to have nonresectable lesions at the time of exploratory laparotomy. CT portography (superior mesenteric arterial portography) is more sensitive (80 to 90%) than CT (70 to 80%) for detection of hepatic metastases, but has a considerable rate of false-positive findings, lowering the positive predictive value.[31-34]

In patients undergoing exploration for recurrent colorectal cancer, the presence of adhesions or the limitations of surgical exposure (transverse upper abdominal incision for liver resection) often preclude a detailed operative staging.

Detection and Staging Recurrent Colorectal Carcinoma with FDG-PET Imaging

A number of studies have demonstrated the role of FDG-PET as a functional imaging modality for detecting recurrent or metastatic colorectal carcinoma.[35-56] Overall, the sensitivity of FDG-PET imaging is in the 90% range and the specificity greater than 70%, both superior to CT.

However, false-negative FDG-PET findings have been reported with mucinous adenocarcinoma. Whiteford and coworkers[57] reported that the sensitivity of FDG-PET imaging for detection of mucinous adenocarcinoma ($n = 16$) is significantly lower than the nonmucinous adenocarcinoma ($n = 93$), 58% and 92%, respectively ($P = 0.005$). They suspect that the low sensitivity of FDG-PET for detection of mucinous adenocarcinoma is due to the relative hypocellularity of these tumors. Similar findings (41% sensitivity) have been reported in a subsequent series of 22 patients.[58]

Several studies have compared FDG-PET and CT for differentiation of scar from local recurrence.[36,37,40-42,46] CT was equivocal in most cases and the accuracy of FDG-PET imaging was greater than 90%. In the largest study (76 patients),[42] the accuracy of FDG-PET and CT were 95% and 65%, respectively. Figure 2 shows an example of a common clinical scenario: a patient is referred with rising CEA levels and a negative conventional workup; local recurrence is demonstrated on FDG-PET-CT images (the color version of this figure is available online). This case also illustrates that concurrent PET-CT imaging permits a definite diagnosis whereas identification of pathological FDG uptake along the transverse colon would be equivocal on PET alone and a subtle soft tissue density at the anastomotic site would be equivocal on CT alone.

Other studies have compared the accuracy of FDG-PET and CT for detection of hepatic metastases.[42,43,45,46,48] Overall, FDG-PET was more accurate than CT. However, most of these studies suffered from a major limitation: PET was performed prospectively while CT was reviewed retrospectively and performed at various institutions, resulting in variable quality. Vitola and coworkers[43] and Delbeke and coworkers[45] reported the comparison of FDG with CT and CT portography. CT portography, which is more invasive and more costly than FDG-PET or CT alone, is regarded as the most effective means of determining resectability of hepatic metastasis by imaging. FDG-PET had a higher accuracy (92%) than CT (78%) and CT portography (80%) for detection of hepatic metastases. Although the sensitivity of FDG-PET (91%) was lower than that of CT portography (97%), the specificity was much higher, particularly at postsurgical sites. A meta-analysis performed to compare noninvasive imaging methods (US, CT, MRI, and FDG-PET) for the detection of hepatic metastases from colorectal, gastric and esophageal cancers demonstrated that at an equivalent specificity of 85%, FDG-PET had the highest sensitivity of 90% compared with 76% for MRI, 72% for CT and 55% for US.[59]

Flanagan and coworkers[47] reported the use of FDG-PET in 22 patients with unexplained elevation of serum CEA level after resection of colorectal carcinoma, and no abnormal findings on conventional workup, including CT. Sensitivity and specificity of FDG-PET for tumor recurrence were 100% and 71% respectively. Valk and coworkers[48] reported sensitivity of 93% and specificity of 92% in a similar group of 18 patients. In both studies, PET correctly demonstrated tumor in two-thirds of patients with rising CEA levels and negative CT scans. An example is illustrated in Fig 2.

Valk and coworkers[48] compared the sensitivity and specificity of FDG-PET and CT for specific anatomic locations and found that FDG-PET was more sensitive than CT in all locations except the lung, where the two modalities were equivalent. The largest difference between PET and CT was found in the abdomen, pelvis and retroperitoneum, where over one-third of PET-positive lesions were negative by CT. PET was also more specific than CT at all sites except the retroperitoneum, but the differences were smaller than the differences in sensitivity. Lai and coworkers[44] in their study of 34 patients found that FDG-PET was especially useful for detecting retroperitoneal and pulmonary metastases. Delbeke and coworkers[45] concluded that outside the liver, FDG-PET was especially helpful in detecting nodal involvement, differentiating local recurrence from postsurgical changes, and evaluating the malignancy of indeterminate pulmonary nodules—indications for which CT has known limitations. In addition, by the nature of being a whole-body technique, FDG-PET imaging allowed identification of distant metastatic disease in the chest, abdomen, or pelvis, which might not be in the field of view of routine CT staging exams.

A meta-analysis of 11 clinical reports and 577 patients determined that the sensitivity and specificity of FDG-PET for detecting recurrent colorectal cancer were 97% and 76% respectively.[60] A comprehensive review of the

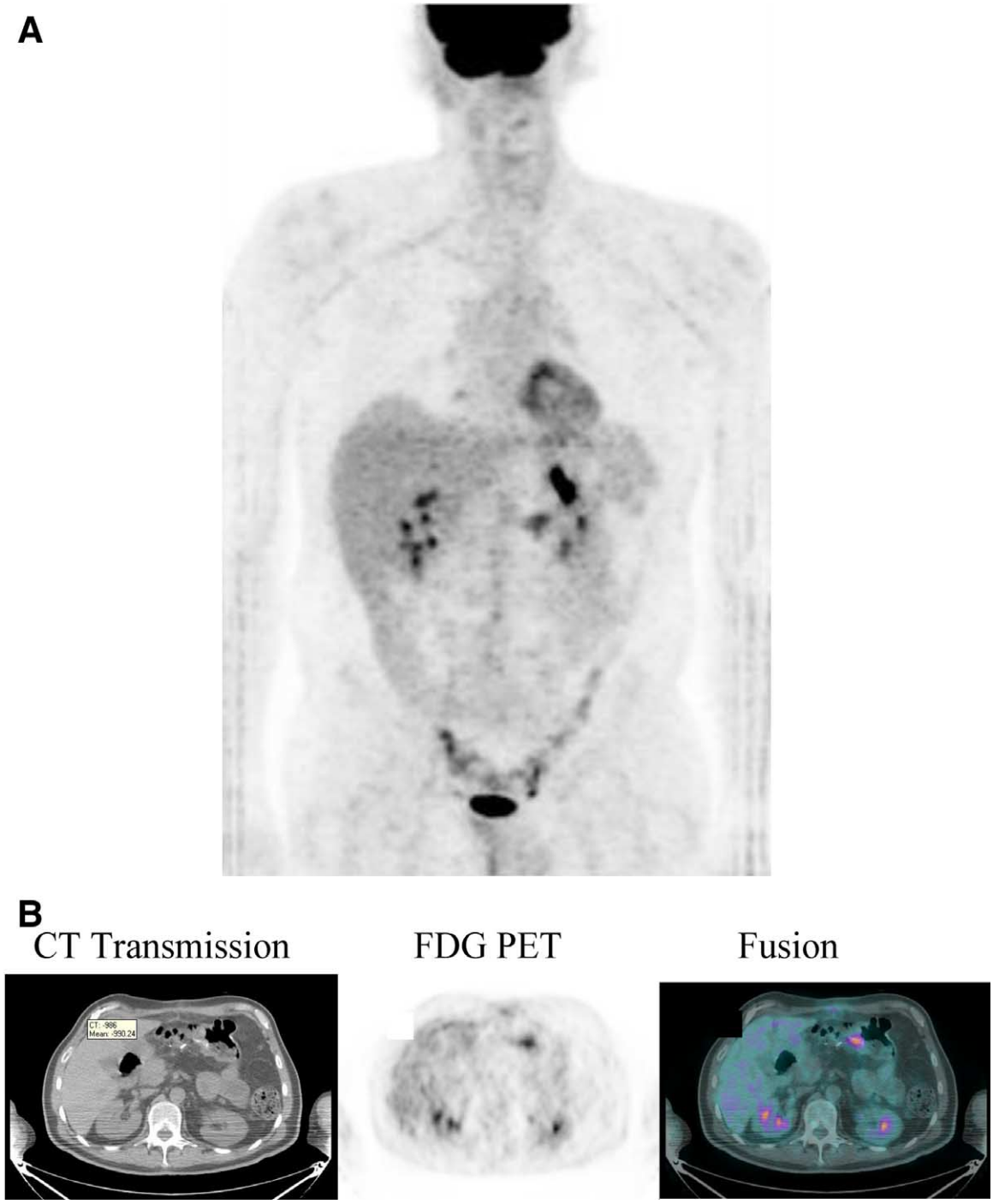

Fig 2. A 63-year-old male with prior colectomy for carcinoma presented with rising serum CEA levels; conventional workup failed to reveal a recurrence. Whole-body positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) imaging was performed using an integrated PET-computed tomography (CT) imaging system providing transmission CT images, FDG-PET images, and fusion images. A, FDG-PET MIP image demonstrates: 1) A focus of uptake in the left upper abdomen projecting over the hilum of the left kidney and 2) Mild FDG uptake along the laparotomy mid-line scar caused by inflammatory changes. B, A PET-CT transaxial view through the right upper pelvis demonstrates that the focus of uptake seen on PET corresponds to the wall of the transverse colon in the region of the anastomosis indicating local recurrence. This case also illustrates that concurrent PET-CT imaging permits a definitive diagnosis whereas identification of pathological FDG uptake along the transverse colon would be equivocal on PET alone and a subtle soft tissue density at the anastomotic site would be equivocal on CT alone.

PET literature (2244 patient's studies) has reported a weighted average for FDG-PET sensitivity and specificity of 94% and 87% respectively compared with 79% and 73% for CT.[61]

Concurrent PET-CT imaging with an integrated system may be especially important in the abdomen and pelvis. PET images alone may be difficult to interpret owing to both the absence of anatomical landmarks (other than the kidneys and bladder), the presence of nonspecific uptake in the stomach, small bowel and colon and urinary excretion of FDG. If possible, images of the abdomen and pelvis should be obtained with the arms elevated to avoid artifacts due to motion and to beam hardening artifacts on the CT transmission images. Concurrent PET-CT imaging is helpful for differentiating focal retention of urine in the ureter for example versus an FDG-avid lymph node. The usefulness of concurrent PET-CT imaging providing fusion images for differentiating physiologic from pathologic FDG uptake in the abdomen has been reported in a study of 28 patients with abdominal tumors[62] and in another study of 10 patients with ovarian malignancies.[63]

A more recent study of 45 patients with colorectal cancer referred for FDG-PET imaging using an integrated PET-CT system concluded that PET-CT imaging increases the accuracy and certainty of locating lesions. In their study, the frequency of equivocal and probable lesion characterization was reduced by 50% with PET-CT compared with PET alone, the number of definite locations was increased by 25%, and the overall correct staging increased from 78% to 89%.[64]

At the time of this writing, most institutions acquire CT transmission images without intravenous contrast to permit optimal attenuation correction but CT images without intravenous contrast do not allow visualization of many hepatic metastases. Therefore, although hepatic metastases are commonly seen as FDG-avid on the PET images, no corresponding lesions are seen on the non-contrasted CT transmission images. A standard of care CT with intravenous and oral contrast need to be performed if surgery is contemplated. Evaluation of the effects of intravenous and oral contrast agents on the attenuation correction of the PET images is ongoing. Intravenous contrast appears as regions of high contrast on CT images, especially during the arterial and arteriovenous phase of enhancement. If these CT images are used for attenuation correction, overcorrection may create artifacts of increased uptake on the FDG-PET images.[65] High-density oral contrast agents[66,67] and metallic implants[68] can create similar artifacts. However, the administration of low-density oral contrast results in only minimal overcorrection and is not believed to interfere with accurate interpretation of the images.[66,66] Review of the images without attenuation correction is helpful to discriminate an overcorrection artifact from "true" uptake; and should be performed if there is abnormal uptake in a region of the body with accumulation of contrast agents or in a region of metallic implants. Nakamoto and coworkers[69] have compared standard uptake value (SUV) measurements on PET images corrected for attenuation with transmission maps obtained using ^{68}Germanium source and CT. They found that CT-based attenuation correction was overestimated by 11% in the skeleton and 2% in soft tissue compared with ^{68}Germanium-based attenuation correction. It is important to take these differences in consideration if the SUV is used when comparing PET studies obtained with different protocols.

Serosal metastases can usually be precisely localized on the surface of the liver. As in the chest, the CT transmission images have to be carefully reviewed for detection of malignant lesions that may not be FDG-avid such as mucinous tumors or renal cell carcinomas for example.

Impact of FDG-PET Findings on Patient's Management

The greater sensitivity of PET compared with CT in diagnosis and staging of recurrent tumor results from two factors: early detection of abnormal tumor metabolism, before changes have become apparent by anatomic imaging, and the whole body nature of PET imaging, which permits diagnosis of tumor when it occurs in unusual and unexpected sites. FDG-PET imaging allows the detection of unsuspected metastases in 13-36% of patients and has a clinical impact in 14 to 65%.[41,42,44-48,50,54-56,70,71] In the study of Delbeke and coworkers,[45] surgical management was altered by PET in 28% of patients, in one-third by initiating surgery and in two-thirds by avoiding surgery. In a survey-based study of 60 referring oncologists, surgeons, and generalists, FDG-PET performed at initial staging had a major impact on the management of colorectal cancer patients and contributed to a change in clinical stage in 42% (80% upstaged and 20% downstaged) and a change in the clinical management in over 60%. As a result of the PET findings, physicians avoided major surgery in 41% of patients for whom surgery was the intended treatment.[72] In a recent prospective study of 51 patients evaluated for resection of hepatic metastases, clinical management decisions based on conventional diagnostic methods were changed in 20% of patients based on the findings on FDG-PET imaging, especially by detecting unsuspected extrahepatic disease.[71] In a meta-analysis of the literature, FDG-PET imaging changed the management in 29% (102/349) patients.[60] The comprehensive review of the PET literature has reported a weighted average change of management related to FDG-PET findings in 32% of 915 patients.[61]

Although survival is not an endpoint for a diagnostic test, Strasberg and coworkers[70] have estimated the survival of patients who underwent FDG-PET imaging in

their preoperative evaluation for resection of hepatic metastases. The Kaplan-Meier test estimate of the overall survival at three years was 77% and the lower confidence limit was 60%. These percentages are higher than those in previously published series that ranged from 30% to 64%. In the patients undergoing FDG-PET imaging before hepatic resection, the three-year disease-free survival rate was 40%, again higher than that usually reported.

Clinical Impact of Concurrent PET-CT Imaging

From the diagnostic point of view, the CT obtained for attenuation maps can also be used for precise localization of the foci of uptake with the help of the fusion of anatomical and molecular images. Published data regarding the incremental value of concurrent PET-CT images obtained with an integrated system compared with PET alone, or compared with PET correlated with a CT obtained at a different time, are limited but conclude the following: 1) Improvement of lesion detection on both CT and FDG-PET images, 2) improvement of the localization of foci of FDG uptake resulting in better differentiation of physiologic from pathologic uptake, and 3) precise localization of the malignant foci, for example in the skeleton versus soft tissue, or liver versus adjacent bowel or node. Concurrent PET-CT fusion images affect the clinical management by guiding further procedures, excluding the need of further procedures, and changing both inter- and intramodality therapy.[73-77] For example, precise localization of metastatic lymph nodes could result in a less invasive and more efficient surgical procedure or guide the biopsy of a mass to FDG-avid regions of the tumor. Concurrent PET-CT fusion images have the potential to provide better maps than CT alone to modulate field and dose of radiation therapy including in patients with colorectal carcinoma.[78,79]

After performing 100 oncology studies using an integrated PET-CT system, the investigators at Pittsburgh University concluded that combined PET-CT images offer significant advantages, including 1) more accurate localization of foci of uptake, 2) distinction of pathologic from physiologic uptake, and 3) improvement in guiding and evaluating therapy.[76,80] A study of 204 patients (34 with gastrointestinal tumors) performed at Rambam Medical Center[81] using an integrated PET-CT system concluded that the diagnostic accuracy of PET is improved in approximately 50% of patients. In that study, PET-CT fusion images improved characterization of equivocal lesions as definitely benign in 10% of sites and definitely malignant in 5% of sites. It precisely defined the anatomic location of malignant FDG uptake in 6% and led to retrospective lesion detection on PET or CT in 8%. The results of PET-CT images had an impact on the management of 14% (28/204) of patients, 7/28 patients with a change of management had colorectal cancer representing 20% (7/34) of patients with gastrointestinal tumors. The changes in management in the 7 patients with colorectal cancer included guiding colonoscopy and biopsy for a local recurrence (n = 2), guiding biopsy to a metastatic supraclavicular lymph node (n = 1), guiding surgery to localized metastatic lymph nodes (n = 3) and referral to chemotherapy (n = 2). Similar conclusions were found in a study of 173 patients performed at Vanderbilt University, 24 of which had colorectal carcinoma.[82]

It is also important to be aware of the potentially useful additional information provided by the independent interpretation by a radiologist experienced in body imaging of the noncontrasted CT portion of the study obtained with integrated PET-CT systems. An analysis of 250 patients demonstrated that these findings are uncommon (3% of patients) but could be important enough to warrant alterations in clinical management.[83]

Cost Analysis

Including FDG-PET in the evaluation of patients with recurrent colorectal carcinoma has been shown to be cost effective in a study using clinical evaluation of effectiveness with modeling of costs and studies using decision tree sensitivity analysis.[48,84,85] In both type of studies, all costs calculations were based on Medicare reimbursement rates and a $1800 cost for a PET scan.

In a management algorithm where recurrence at more than one site was treated as nonresectable, Valk and coworkers[48] evaluated cost savings in 78 patients undergoing preoperative staging of recurrent colorectal carcinoma. This study was limited to preoperative patients, and demonstrated potential savings of $3003/patient resulting from diagnosis of nonresectable tumor by PET.

In 1997, Gambhir and coworkers[84] used a quantitative decision tree model combined with sensitivity analysis to evaluate cost issues if all patients presenting with recurrent colorectal cancer undergo FDG-PET imaging. The conventional strategy for detection of recurrence and determination of resectability using CEA levels and CT was compared with the conventional strategy plus PET for all patients presenting with suspected recurrence. The assumptions included prevalence of resectable disease of 3%, sensitivity and specificity of 65% and 45% respectively for CT, and 90% and 85% for PET. The conventional strategy plus PET showed an incremental saving of $220/patient without a loss of life expectancy.

Park and coworkers[84] used the decision tree sensitivity analysis to evaluate the cost of adding FDG-PET imaging in the evaluation of patients referred for suspected recurrence based on elevated CEA levels and candidates for hepatic resection. The CT plus PET strategy was higher in mean cost by $429 per patient, but

resulted in an increase in the mean life expectancy of 9.5 days per patient.

FDG IMAGING TO MONITOR THERAPY OF COLORECTAL CARCINOMA

FDG-PET is most helpful to monitor patients with advanced-stage colorectal carcinoma that is associated with a poor prognosis. Systemic chemotherapy with 5-fluorouracil often in combination with radiotherapy has demonstrated effective palliation and improved survival.[86] A preliminary study on 6 patients demonstrated the FDG uptake decreased in the primary tumor during radiation therapy whereas the size did not change on CT.[87] Another study of 44 patients demonstrated that FDG-PET imaging can differentiate local recurrence from scarring after radiation therapy.[88] However, increased FDG uptake immediately following radiation may be due to inflammatory changes and is not always associated with residual tumor. The time course of postirradiation FDG activity has not been studied systematically; it is, however, generally accepted that FDG activity present six months after completion of radiation therapy most likely represents tumor recurrence. A case-controlled study of 60 FDG-PET studies performed 6 months following external beam radiation therapy for rectal cancer found a sensitivity of 84% and specificity of 88% for detection of local pelvic recurrence.[89] A pilot study of 15 patients with primary rectal carcinoma demonstrated that FDG-PET imaging adds incremental information for assessing the response to preoperative radiation and 5-fluorouracil-based chemotherapy.[90]

Hepatic metastases can be treated with systemic chemotherapy or regional therapy to the liver. A variety of procedures to administer regional therapy to hepatic metastases have been investigated including chemotherapy administered through the hepatic artery using infusion pumps, selective chemoembolization, radiofrequency ablation, cryoablation, alcohol ablation and radiolabeled ^{90}Y-microspheres.[91-94] There are preliminary reports suggesting that the response to chemotherapy in patients with hepatic metastases can be predicted with PET. Responders may be discriminated from nonresponders after four to five weeks of chemotherapy with fluorouracil by measuring FDG uptake before and during therapy.[95] Regional therapy to the liver by chemoembolization can also be monitored with FDG-PET imaging as shown by Vitola and coworkers[96] and Torizuka and coworkers.[97] FDG uptake decreases in responding lesions and the presence of residual uptake in some lesions can help in guiding further regional therapy. Langenhoff and coworkers[98] have prospectively monitored 23 patients with liver metastases following radiofrequency ablation and cryoablation. Three weeks after therapy, 51/56 metastases became FDG negative, and there was no recurrence during 16 months follow-up; whereas among the 5/56 lesions with persistent FDG uptake, 4/5 recurred. Data in smaller series of patients supports their findings.[99,100] Figure 3 illustrates residual/recurrent tumor adjacent to a site of radiofrequency ablation detected on FDG-PET but not on the CT images (the color version of this figure is available online). Wong and coworkers[101] have compared FDG-PET imaging, CT or MRI and serum levels of CEA to monitor the therapeutic response of hepatic metastases to ^{90}Y-glass microspheres. They found a significant difference between the FDG-PET changes and the changes on CT or MRI; the changes in FDG uptake correlated better with the changes in serum levels of CEA. Figure 4 illustrates the use of FDG-PET imaging to monitor the efficacy of regional therapy to the liver with ^{90}Y-microspheres. In summary, preliminary data suggest that FDG-PET imaging may be able to effectively monitor the efficacy of regional therapy to hepatic metastases but these data need to be confirmed in larger series of patients.

LIMITATIONS OF FDG IMAGING

Tumor detectability depends on both the size of the lesion and the degree of uptake, as well as surrounding background uptake and intrinsic resolution of the imaging system. False-negative lesions can be the result of partial volume averaging, leading to underestimation of the uptake in small lesions (less than twice the resolution of the imaging system) or in necrotic lesions with a thin viable rim, falsely classifying these lesions as benign instead of malignant. The sensitivity of FDG-PET for detection of mucinous adenocarcinoma is lower than for nonmucinous adenocarcinoma (41-58% versus 92%), probably because of the relative hypocellularity of these tumors.[57,58]

In view of the known high uptake of FDG by activated macrophages, neutrophils, fibroblasts and granulation tissue, it is not surprising that inflamed tissue demonstrates FDG activity. Mild-to-moderate FDG activity seen early after radiation therapy, along recent incisions, infected incisions, biopsy sites, drainage tubing and catheters, as well as colostomy sites can lead to errors in interpretation if the history is not known. Some inflammatory lesions, especially granulomatous ones, may be markedly FDG-avid and can be mistaken for malignancies; this includes inflammatory bowel disease.

FDG uptake normally present in the gastrointestinal tract can occasionally be difficult to differentiate from a malignant lesion. Incidental colonic FDG uptake in 27 patients without colorectal carcinoma has been correlated with colonoscopic and/or histolopathologic findings.[102] Diffuse uptake in 8 patients was normal and associated with a normal colonoscopy. Segmental uptake was due to colitis in 5/6 patients. Focal uptake in 7 patients was associated with benign adenomas. The clinical history, physical examination, pattern of uptake and correlation with anatomy as seen on the CT images

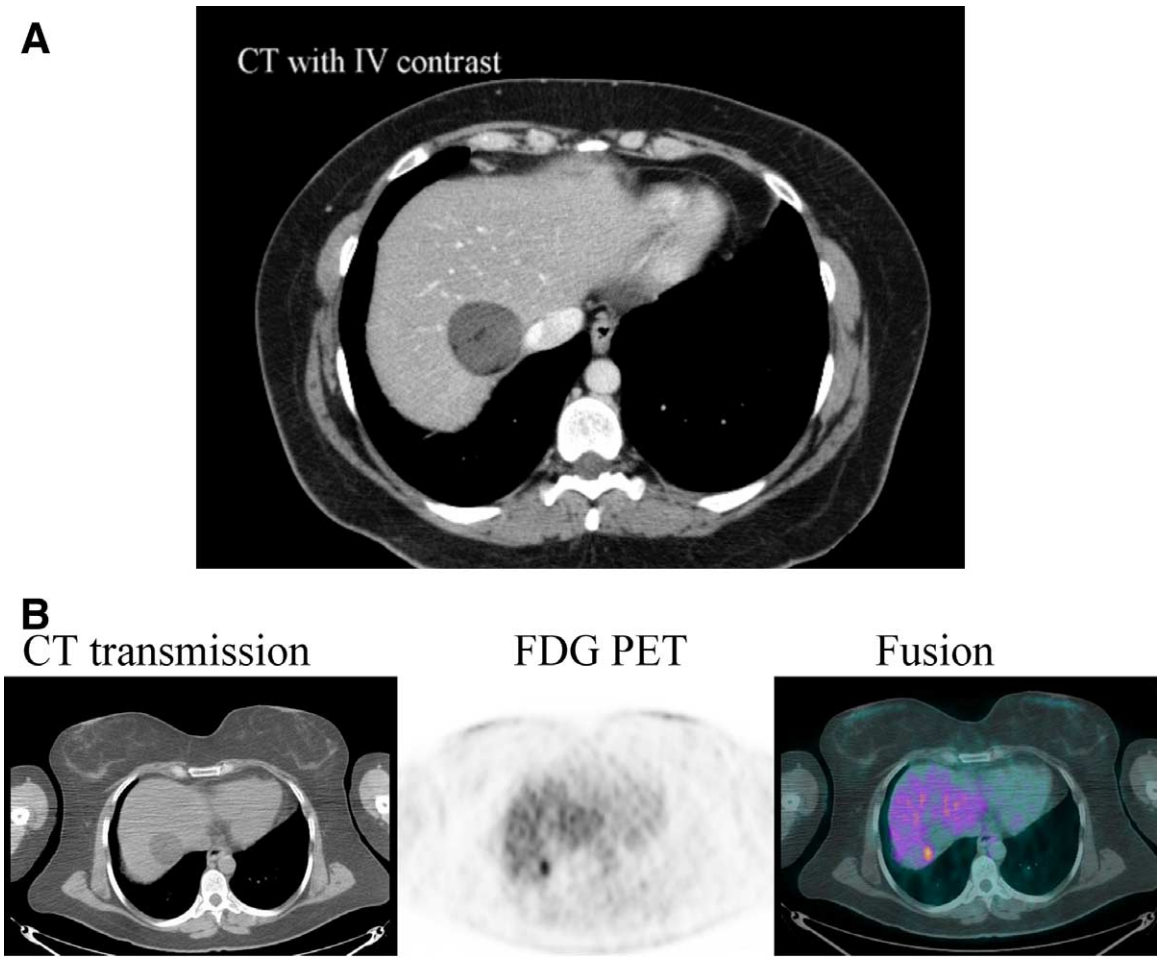

Fig 3. A 46-year-old female with a history of colon cancer presented with a liver metastasis and underwent treatment with radiofrequency ablation. Contrast-enhanced CT and positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) imaging with an integrated PET-computed tomography (CT) imaging system were performed 2 months after therapy. A, The CT with contrast revealed necrosis corresponding to the previously seen hepatic metastasis at the dome of the liver. B, A corresponding PET-CT transaxial view through the dome of the liver reveals a focus of FDG uptake adjacent to the region of necrosis observed on CT, indicating persistent/recurrent tumor.

are more helpful in avoiding false-positive interpretations than semiquantitative evaluation by SUV.

COST AND REIMBURSEMENT ISSUES

Until recently, the implementation of clinical PET was hindered by the high cost of PET systems, the need for access to a cyclotron and support laboratory for FDG production, high maintenance and operating expenses of scanners and cyclotrons, and lack of reimbursement for clinical procedures by third-party payers. The third-party reimbursement situation for oncologic PET has improved in recent years. In July 2001, the Center for Medical Services approved and implemented reimbursement by Medicare for six types of malignant tumors including colorectal carcinoma. This coverage is for diagnosis, staging and restaging, but not monitoring therapy.

POTENTIAL NEW PET TRACERS FOR CLINICAL USE

Besides evaluation of glucose metabolism with FDG, PET can assess various other biologic parameter such as perfusion, metabolism of other compounds, hypoxia and receptor expression. Some of these radiopharmaceuticals are labeled with positrons emitters that have a short half-life, such as ^{15}O (T1/2 = 2 min), ^{13}N (T1/2 = 10 min), and ^{11}C (T1/2 = 20 min). The short half-life of these radioisotopes prevents any timely distribution of the radiopharmaceuticals labeled with them and therefore, their use is restricted to institutions having a cyclotron and associated laboratories and personnel on-site. Some tracers labeled with ^{18}F, such as ^{18}F-fluorothymidine (FLT), currently are investigated for

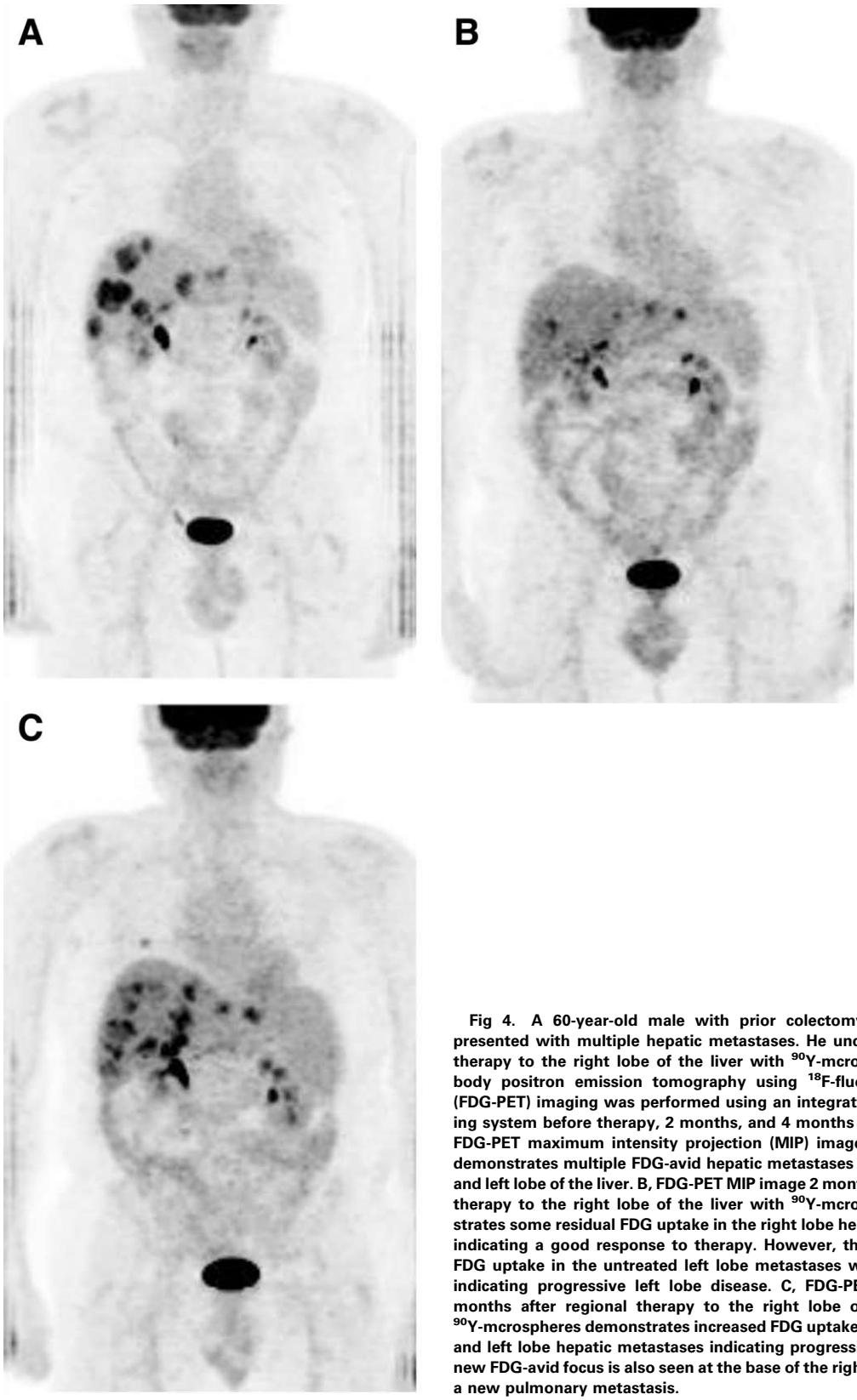

Fig 4. A 60-year-old male with prior colectomy for carcinoma presented with multiple hepatic metastases. He underwent regional therapy to the right lobe of the liver with ^{90}Y-mcrospheres. Whole-body positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) imaging was performed using an integrated PET-CT imaging system before therapy, 2 months, and 4 months after therapy. A, FDG-PET maximum intensity projection (MIP) image before therapy demonstrates multiple FDG-avid hepatic metastases in both the right and left lobe of the liver. B, FDG-PET MIP image 2 months after regional therapy to the right lobe of the liver with ^{90}Y-mcrospheres demonstrates some residual FDG uptake in the right lobe hepatic metastases indicating a good response to therapy. However, there is persistent FDG uptake in the untreated left lobe metastases with a new focus indicating progressive left lobe disease. C, FDG-PET MIP image 4 months after regional therapy to the right lobe of the liver with ^{90}Y-mcrospheres demonstrates increased FDG uptake in both the right and left lobe hepatic metastases indicating progression of disease. A new FDG-avid focus is also seen at the base of the right lung indicating a new pulmonary metastasis.

clinical use and may have applications for evaluation of patients with colorectal carcinoma.

Tracer of Bone Metabolism

^{18}F-fluoride was first described as a skeletal imaging agent in the 1960's but then was replaced by the ^{99m}Tc-labeled diphosphonate radiopharmaceuticals.[103] With the widespread applications of FDG-PET in oncology, PET imaging systems are becoming more widely available, and there is a renewed interest in^{18}F-fluoride. Although the mechanism of uptake for ^{18}F-fluoride is similar to that for other bone-imaging radiopharmaceuticals,[104] the spatial resolution of the PET technology is superior to that of both planar and SPECT imaging using the ^{99m}Tc-radiopharmaceuticals. Because of the better spatial resolution and routine acquisition of tomographic images, ^{18}F-fluoride PET imaging offers potential advantages over bone scintigraphy in detecting metastases. In a study of 44 patients, Schirrmeister and coworkers[105] demonstrated that twice as many benign and malignant lesions were detected with ^{18}F-fluoride PET compared with planar scintigraphy. It was also possible to better differentiate benign from malignant lesions with PET because of the better resolution, particularly in the spine. In a further study, the same authors demonstrated the greater accuracy of ^{18}F-fluoride PET leading to a change of management in a group of patients with breast cancer.[106] Although skeletal metastases are not common in colorectal cancer, ^{18}F-fluoride may have a role in the future if skeletal metastases are suspected clinically.

Tracers of DNA Synthesis

The rate of DNA synthesis can be assessed using ^{11}C-thymidine or FLT. Thymidine is a DNA precursor and allows direct assessment of tumor proliferation. In the early nineties, Higashi and coworkers[107] demonstrated that in vitro uptake correlates with the tumor proliferative rate. Then, other investigators demonstrated in an animal tumor model that uptake of ^{11}C-thymidine correlated with viable tumor cells better than FDG uptake cells after fractionated radiotherapy.[108] More recently, Shields and coworkers[109] have developed and evaluated ^{18}FLT, a more promising radiopharmaceutical for clinical use because of its ^{18}F labeling. Dittman and coworkers[110] evaluated 16 patients with thoracic tumors using both FLT and FDG. Compared with FDG, FLT uptake was lower but with a significant linear correlation. The authors concluded that FLT PET accurately visualizes thoracic tumors but that in the liver and bone marrow, high physiologic uptake prevents detection of metastases. On the other hand, FLT may be favorable for imaging cerebral metastases owing to the low physiologic uptake. A report of 17 patients with colorectal cancer comparing FDG and FLT demonstrated all primary tumors were visualized with both tracers but FDG uptake was on average two-fold higher with FDG compared with FLT.[111] Pulmonary and peritoneal metastases were visualized with both tracers, but the sensitivity of FLT for hepatic metastases was only 34% compared with 97% for FDG. This was due to the high physiologic hepatic background activity with FLT. Therefore, the authors concluded that it was unlikely that FLT would play an important role for evaluation of patients with colorectal carcinoma.

Labeled Drugs

5-Fluorouracil is the mainstay chemotherapeutic agent for treatment of colorectal carcinoma and ^{18}F-5-fluorouracil is biochemically similar to 5-fluorouracil. Utilizing a kinetic modeling approach with^{18}F-fluorouracil, PET imaging has been used to study the influence of the biomodulator folinic acid on intracellular trapping of 5-fluorouracil within hepatic metastases with the expectation that this would correlate with the therapeutic effect.[112] Trapping within hepatic metastases can be variable and ^{18}F-5-fluorouracil PET can predict the response to therapy and prognosis.[113,114]

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