The Role of Positron Emission Tomography in Colorectal Carcinoma

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Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) is a functional imaging modality that provides mapping of glucose metabolism in the whole body. The glucose analogue fluorodeoxyglucose is labeled with the cyclotron-produced, positron-emitting radioisotope fluorine-18. The resulting radiopharmaceutical FDG is a substrate for glucose transport proteins (Glut) in cell membranes and accumulates intracellularly. Increased metabolic activity in malignant tissue is accompanied by increased glucose uptake relative to that of surrounding normal tissue. This focal increase in glucose uptake can be identified with FDG PET, which allows identification of malignant tumor foci. Multiple reports have shown that positron emission tomography with 18F-fluorodeoxyglucose scanning (FDG-PET) is highly accurate in detecting early localized tumor recurrence with a sensitivity and specificity in the mid nineties. FDG-PET scanning evaluates abdomen, chest, and pelvis in one examination setting, permiting identification of local recurrence as well as distant metastasis. FDG-PET is also highly sensitive in detecting hepatic and extra-hepatic metastasis. Finally, FDG-PET scanning can distinguish post-treatment (postoperative and postradiation therapy) scarring from recurrent tumors since malignant tumors are metabolically active and FDG-avid on PET imaging and scar tissue is not. This high accuracy in identifying early stage recurrent tumors with FDG-PET is crucial for potential surgical cure and improving patient outcomes.

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With 130,000 to 165,000 new cases diagnosed each year in the United States, colorectal carcinoma (CRC) is a major health problem and the second leading cause of cancer death in the US and Europe (1). CRC frequently metastasizes to distant sites. The most common sites are the liver followed by lung, bone, brain, and ovaries. Less frequent sites reported include adrenal, testicular, umbilical, and skin (2,3). In advanced disease, CRC can even invade viscera throughout the peritoneal cavity. At the time of diagnosis, CRC is localized in only 36% of patients; regional lymph node metastases are present in 39% and distant metastases are present in 19% (4). Of patients who undergo surgical resection, 20%-40% develop a local recurrence within 2 years (5,6). Since metastatic colorectal cancer is potentially treatable and curable (7), the most valuable diagnostic information is obtained from the test that most accurately identifies all metastatic foci, and at the same time is specific enough to prevent invasive procedures in those patients free of disease. A test with high sensitivity that lacks specificity may lead to expensive, invasive, and unnecessary procedures in many patients. Other patients with potentially curable recurrent disease may be denied the chance of surgery due to the false diagnosis of extensive inoperable disease.

On the basis of conventional presurgical staging techniques, such as CT, the 5-year disease-free survival rate after attempted curative resection can be as low as 20% (20%-40%). It is essential to improve the accuracy of the preoperative initial staging and detection of recurrent tumors. There is, therefore, a need to explore the role of newer imaging techniques such as PET scanning to help early detection and prompt treatment of recurrences that ultimately may lead to cure in a higher percentage of CRC patients.

Rationale for PET with FDG

The rationale for tumor imaging with 18F-fluorodeoxyglucose (FDG) is based on a fundamental property of tumors, namely, increased glucose metabolism. This process begins when tumor cells take up and shuttle FDG into glycolysis. Both deoxyglucose and fluorodeoxyglucose are distributed in the blood and taken up into the cell by active transport via noninsulin-dependent transmembrane proteins Glut I and Glut III. The enzyme hexokinase, the first step in the glycolytic pathway, phosphorylates the FDG to the 6-phosphate form FDG-6-phosphate (FDG-6P). The FDG-6P is not a suitable substrate for the action of glucose-6-isomerase, the subsequent metabolic step of glycolysis. The only way for the

FDG-6P to leave the cell is after breakdown by phosphorylase enzymes (glucose-6-phosphatase) that can catabolize the FDG-6P to FDG. However, the concentration of glucose-6-phosphatase is very low in most glucose avid tissues (except in the hepatocyte), and the reverse transformation is slow. For this reason FDG-6-P remains trapped within tissues (such as tumor, brain, heart), which have active glycolysis, and progressively accumulates in the cell over time in rate that is proportional to the rate of glycolysis.

PET FDG Indications for CRC

The established indications for FDG-PET imaging in CRC include (presently reimbursed): Initial Diagnosis, Staging, and Re-staging. The expectation of cure depends on the stage of the initial tumor. Assessment of tumor extent and the presence or absence of adenopathy are essential to the determination of prognosis and the risk for tumor recurrence. Primary tumors confined to the submucosa are cured in more than 90% of cases, and the risk for tumor recurrence is only 5% (4,5). FDG-PET imaging is best used to more accurately stage disease before attempted curative resection or to confirm equivocal findings on conventional anatomical imaging studies before initiating treatment (8). FDG-PET has very good sensitivity (89%-91%) and is more accurate than CT for the detection of liver metastases (9). FDG imaging has also been shown to be superior to conventional imaging for detecting extrahepatic metastases with a sensitivity of 94% versus 67% for conventional imaging (8). FDG-PET can change patient management in 26%-65% of cases by identifying a resectable or nonresectable metastasis that was unsuspected clinically, not seen, or equivocal on CT. Seltzer et al demonstrated that changes in the clinical stage were reported for 42% of the patients, and, among these, the disease was upstaged in 80% and downstaged 20% of the cases. Furthermore, In cases of recurrent disease, PET contributed to intermodality (e.g. surgery to radiation) management changes in 37% of the patients, and to intramodality (e.g. types of chemotherapeutic agents) changes in 18% of the cases (6,8-11).

FDG-PET in Restaging CRC

Although there has been controversy as to the role of intensive follow-up in colorectal cancer patients, a recent meta-analysis has shown a beneficial role (12). In patients who undergo curative surgery, approximately 40% will demonstrate recurrence within 2 years of diagnosis. Noninvasive differentiation between malignant and benign lesions in suspected recurrent CRC remains a diagnostic challenge. The currently used anatomically based imaging modalities are CT, ultrasound, and magnetic resonance imaging (MRI), all of which are fairly sensitive but poorly specific. The challenge increases significantly when the area in question is a postsurgical site, where fibrosis and scar formation may be present. At present, no general consensus exists on how to follow-up and monitor those patients. The lack of accuracy of tumor markers and the inconsistent use of different imaging techniques (CT, MRI, ultrasound, etc.) are likely the main reasons for the currently nonstandardized postsurgical care.

Several methods are used for monitoring recurrences after resection of CRC. When recurrent disease is recognized, it is frequently advanced and carries a poor prognosis (13). Measurement of serum levels of carcinoembryonic antigen (CEA) has a reported sensitivity of only 59% and specificity of 84% for detection of recurrences. Also, CEA may detect recurrence but does not show the site in question, and the disease may not be resectable (14). CT is helpful in evaluating liver metastases, but has limited use in the evaluation of isodense hepatic lesions or for differentiating postsurgical changes from tumor recurrence (15). A study by Gupta et al reported a sensitivity and specificity of CT as low as 42% and 50%, respectively, for detection of liver metastases (16). There are many reports of FDG-PET detecting clinically silent recurrent disease in patients with increasing CEA and negative CT scans (17). Several studies have demonstrated that as a metabolic-based imaging technique FDG-PET is both highly sensitive and specific in differentiating recurrence from postoperative fibrosed tissue. FDG-PET's reported sensitivity is between 95% and 100% and specificity between 86% and 100%. The positive and negative predictive values are 88% and 92%, respectively, for the detection of local recurrence whereas the sensitivity for CT and colonoscopy was in the seventies (8,18,19). Ito et al studied 15 patients with suspected recurrent rectal carcinoma and demonstrated that FDG-PET was superior to MRI for detecting recurrences in the pelvis and reliably differentiated scar from recurrent tumor in all patients (20). A study by Strauss et al showed that out of 29 patients with suspected local recurrent CRC, all local recurrent malignancies were visible with FDG-PET and had at least twice the uptake of the radiopharmaceutical in comparison to the uptake of scar or soft tissue (19,21). FDG imaging can also be used to differentiate local recurrence from scarring following radiation therapy with a sensitivity of up to 90%. FDG accumulation within an abnormality is strongly suggestive of tumor recurrence. Absence of tracer uptake indicates lack of disease, and these patients can be followed with observation (4,9,10). Finally, in many studies, FDG-PET imaging not only had a high sensitivity and specificity for recurrent CRC, but also, and more importantly, PET changed the surgical management in more than 25% of the patients (22). Falk et al demonstrated that PET was superior to CT in the preoperative staging of 16 patients with primary or recurrent colorectal cancer, with a predictive accuracy of 83% for PET and 56% for CT (23).

FDG-PET in the Selection of Patients for Resection of Hepatic Metastases

Colorectal cancer is the most common metastatic cancer to occur in the liver. Partial hepatic resection, consisting of removing all anatomically resectable liver lesions and leaving sufficient disease-free liver tissue to allow normal hepatic function, is established as the optimal treatment (24-26). In some patients, surgical resection can prolong survival and improve quality of life (27,28). Preoperatively unidentified extrahepatic disease is responsible for relapse in approximately 50% of patients who have undergone partial hepatic resection (29,30). Therefore, candidates for this major surgical procedure should have anatomically resectable liver lesions and be free of extrahepatic disease. It must be emphasized that the role of preoperative imaging in patient selection is capital. First, it will identify the subgroup of patients who may benefit from surgery, and it should help to prevent unnecessary radical surgery in those who won't (31), especially if the operative mortality could be as high as 7% (30). FDG-PET can improve the selection of patients for partial hepatic resection by optimizing the detection of extrahepatic tumor foci throughout the body and thereby reduce the morbidity and mortality associated with inappropriate surgery (32). One recent series has shown improved survival rates among patients who underwent FDG-PET prior to partial hepatic resection (33).

Case reports

The following six cases illustrate the use of FDG-PET in staging and restating CRC patients, as well as in selecting patients who are potential candidates for partial hepatic or pulmonary resection. Emphasis is placed on the evaluation of extrahepatic disease sites, which is where the real strength of FDG-PET has been shown to lie.

Case 1:

A 70-year-old male with colon cancer and left hemicolectomy had a kidney transplant in 1997. A recent CT scan showed liver lesions. FDG-PET scan was obtained to determine resectability of the liver lesions. FDG-PET images (Figure 1) demonstrate multiple intense areas of focal hypermetabolism in the liver in variable sizes. The largest lesions show that central photopenia corresponds to central necrosis. The uptake and the excretion of the tracer in the right pelvis correspond to the right pelvic transplanted kidney. Following the results of the FDG-PET scan, it was concluded that the patient is not a candidate for partial liver resection.

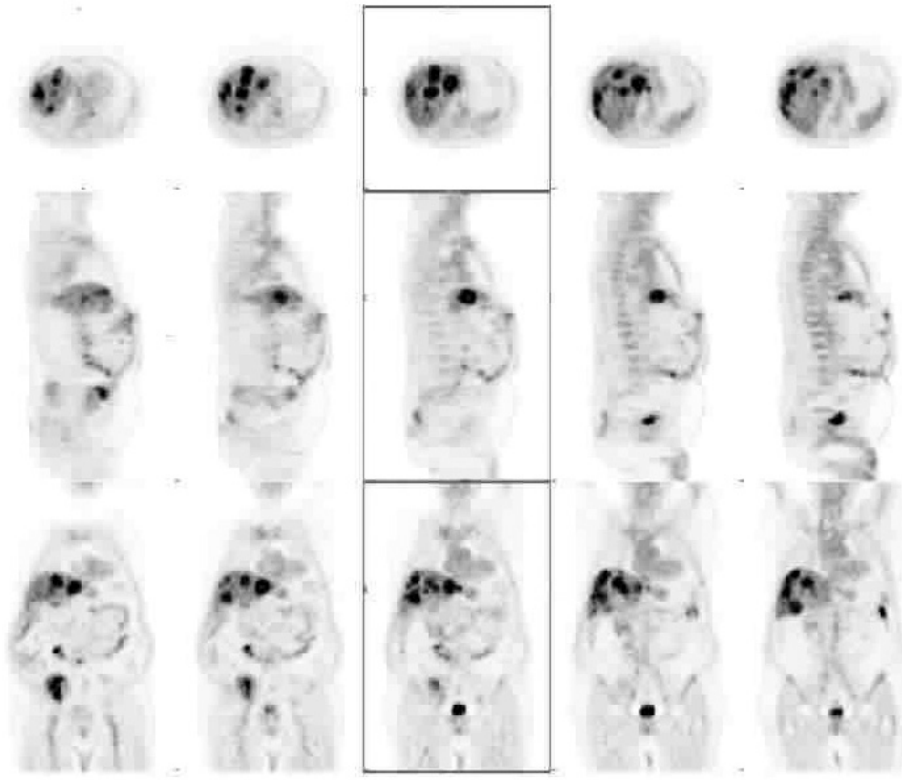

Figure 1: After the injection of 15.45 mci IV of f18 FDG IV, positron emission tomography images were obtained of the whole body from the neck to the pelvis. Transaxial, sagittal, and coronal images (top to bottom) demonstrate multiple intense areas of focal hypermetabolism in the liver in variable sizes.

Case 2:

A 54-year-old male with colon cancer underwent a partial resection in December of 1998. Follow-up CT scan showed liver lesions. FDG-PET scan obtained for restaging showed physiologic distribution of tracer in the thorax, abdomen, and pelvis (Figure 2). Special attention was given to the liver, which showed no focal areas of hypermetabolism to suggest metastatic disease. It was concluded following the FDG-PET scan that liver lesions seen on CT most likely represent benign cysts. This was confirmed by aspiration during surgery.

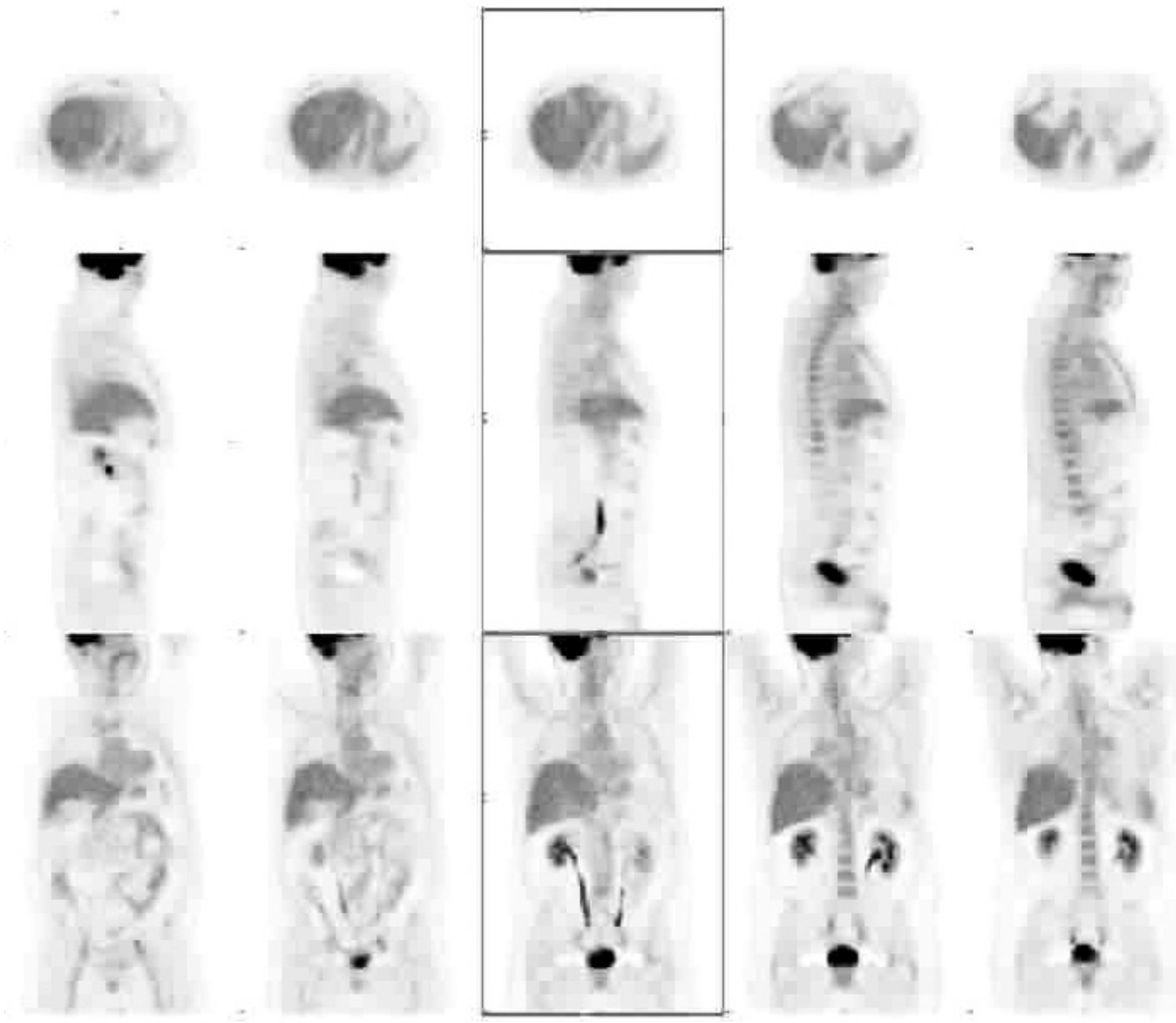

Figure 2: After the injection of 14.2 mci IV of FDG, positron emission tomography images were acquired. Transaxial, sagittal, and coronal images (top to bottom) demonstrated no abnormal areas of hypermetabolism.

Case 3:

A 66-year-old female with colon cancer underwent a right partial hemicolectomy in December 2001. A recent CT scan showed suspicious liver lesions and positive retroperitoneal nodes (more than 1 cm in diameter). FDG-PET scan for restaging (evaluation for reccurence) and characterization of the liver lesions revealed multiple intense lesions of various sizes in the liver (Figure 3). Otherwise, there was no evidence of any abnormality seen in the thorax, abdomen, or pelvis. Physiologic distribution of tracer was seen in the retroperitoneum with no abnormalities to suggest metastatic lymphadenopathy. Furthermore, the suspect node detected on CT was not metabolically active. Consequently, the patient was still a candidate for partial hepatectomy since there was no evidence of extrahepatic disease.

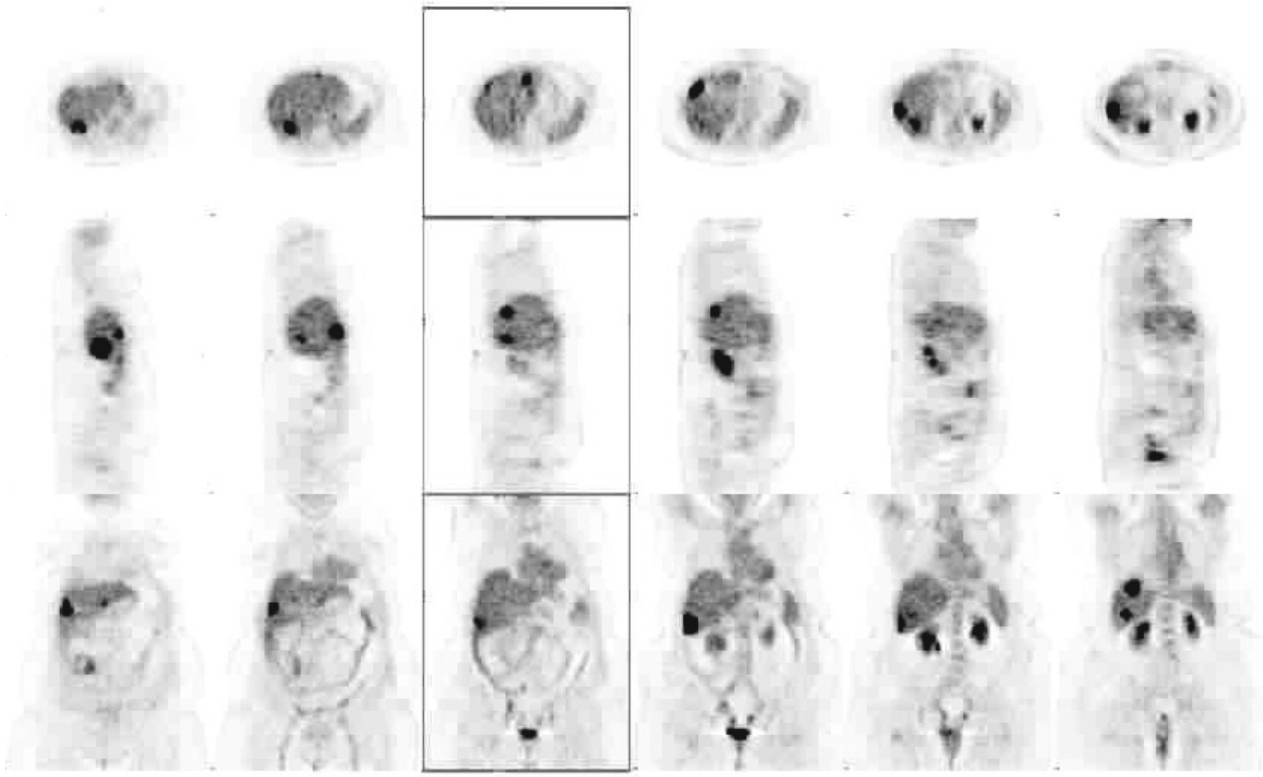

Figure 3: After the injection of 16 mci IV of FDG, positron emission tomography images were obtained from the neck to the proximal thigh. Transaxial, sagittal, and coronal images (top to bottom) revealed hypermetabolic lesions of the liver consistent with metastatic disease. Otherwise, no evidence of any abnormality was seen in the thorax, abdomen, or pelvis.

Case 4:

A 41-year-old female with history of colon cancer, status post-total colectomy with ileal pouch reconstruction. A follow-up CT scan showed stable postoperative changes within the pelvis unchanged from the previous examination and no clear evidence of recurrence, metastatic disease, or lymphadenopathy. A FDG-PET scan was obtained for further evaluation and revealed (Figure 4) areas of hypermetabolism in the pelvis and the retroperitonium suspicious for local recurrence and paraaortic metastatic lymphadenopathy, respectively. The patient underwent an exploratory surgery in December 2001 that revealed macroscopic reccurence in the distal ileum and pelvis.

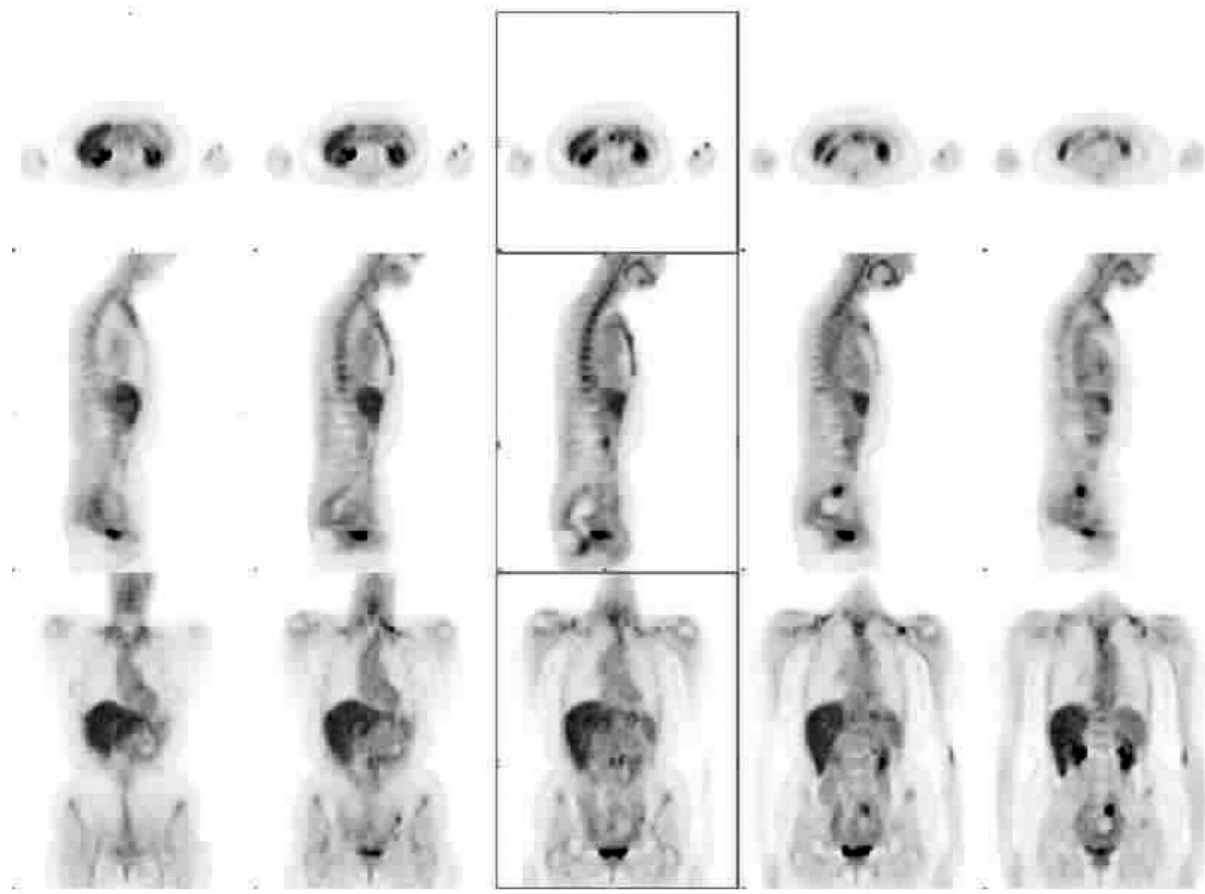

Figure 4: The patient received 16.3 mci IV of FDG approximately 60 minutes before the scan. Whole body positron emission tomography images were obtained from the neck to the midthigh. The transaxial, sagittal, and coronal images demonstrate two focal areas of intense increased uptake in the left pelvic area. The standardized uptake values of these lesions are 2.9 and 2.8, respectively. Also, there are two areas of increased uptake in the left and right paraaortic regions at the level of the mid-kidneys. Retrospective comparison with the CT scan (not shown) correlated with the paraaortic nodes. However, the left hemipelvic abnormalities were not seen on CT.

Case 5:

A 67-year-old female with history of colon cancer and left colectomy underwent a mobilization of splenic flexure in November 1997. On follow-up examination, the patient was noted to have rising CEA level. CT scan showed left hilar mass of approximately 2 x 3 cm and a right apical nodule of 0.8 cm. FDG-PET was obtained for further restaging and for the evaluation of the lung lesions that revealed two focal areas of hypermetabolism consistent with malignancy in the left hilum and the apex of the right lung, respectively (Figure 5). Otherwise, there was no evidence of any abnormality in the mediastinum, abdomen, or pelvis. The patient underwent left paramedian sternotomy with pleurotomy and left upper lobe lung biopsy that demonstrated adenocarcinoma compatible with colonic origin.

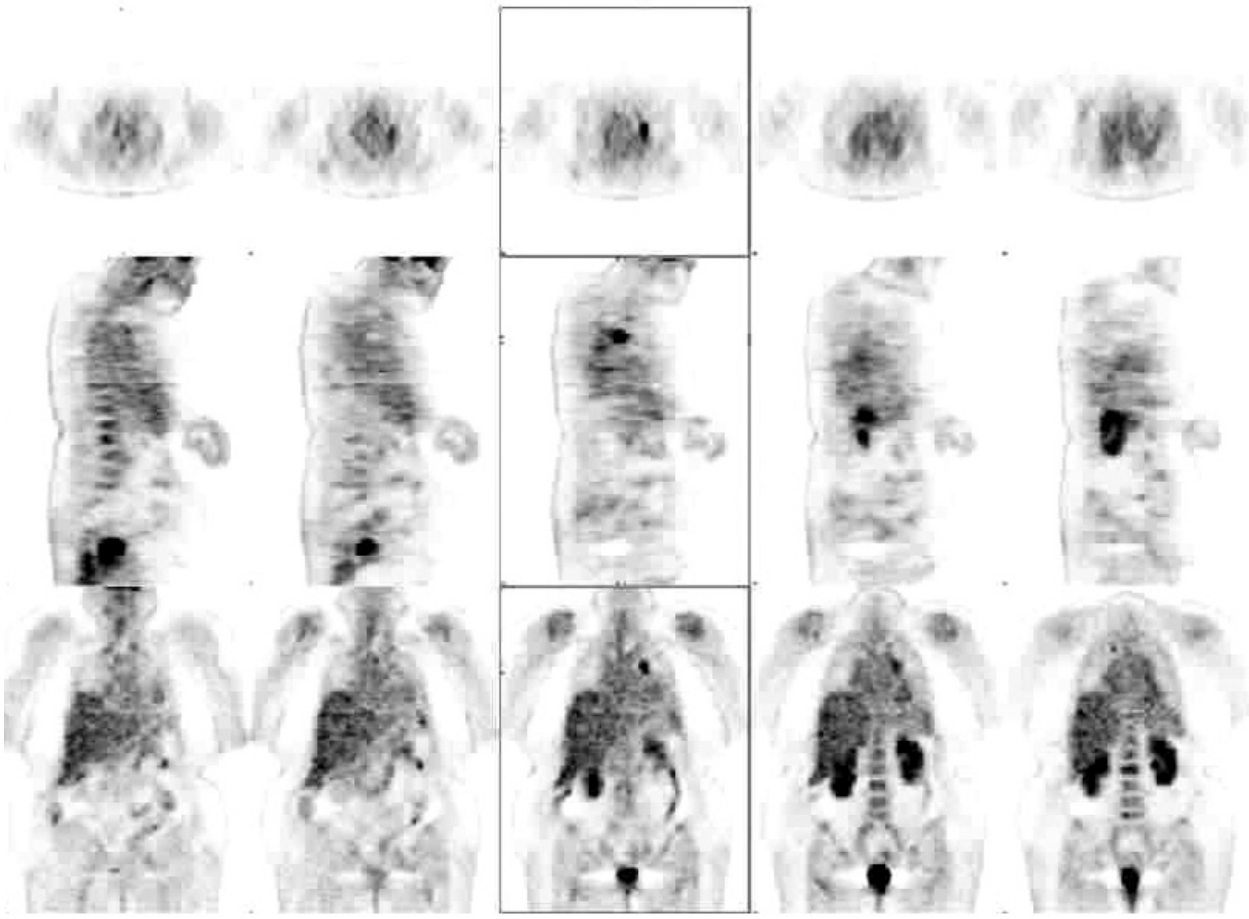

Figure 5: Positron emission tomography images were obtained 60 minutes after the injection of 15 mci IV of f-18 FDG. The transaxial, sagittal, and coronal images (top to bottom) demonstrate intense focus of increased metabolism in the left hilar region and a smaller and less intense area of focal uptake at the apex of the right lung. The standardized uptake value (SUV) of the left hilar lesion is 6.7. The SUV of right apical nodule is 2.4. However, since this lesion is under 1 cm in diameter, the standardized uptake values is probably underestimated secondary to partial volume effect. Otherwise, there is no evidence of any abnormality in the mediastinum, abdomen, or pelvis.

Case 6:

A 66-year-old male with colon cancer underwent sigmoidectomy and chemotherapy in October 1997. The patient has been followed for the past 4 years and on a recent control CT scan was found to have a right upper-lobe mass and multiple small equivocal lesions throughout the liver. FDG-PET scan was obtained for more complete restaging and for the evaluation of the lung and liver abnormalities seen on the recent CT scan. The FDG-PET study demonstrated a focal area of hypermetabolism seen in the right upper lobe posteriorly that is compatible with metastatic disease (Figure 6). Otherwise, there was no evidence of any suspicious abnormalities in the mediastinum, retroperitoneum, abdomen, or pelvis. The liver showed normal tracer distribution. Subsequently, the liver lesions seen on CT were felt to be benign. Tissue diagnosis of the lung was consistent with metastatic adenocarcinoma. Following the FDG-PET result, the patient was a candidate for surgery and underwent right bilobectomy (right upper and right middle lobectomy). Mediastinal lymph node sampling revealed no evidence of disease.

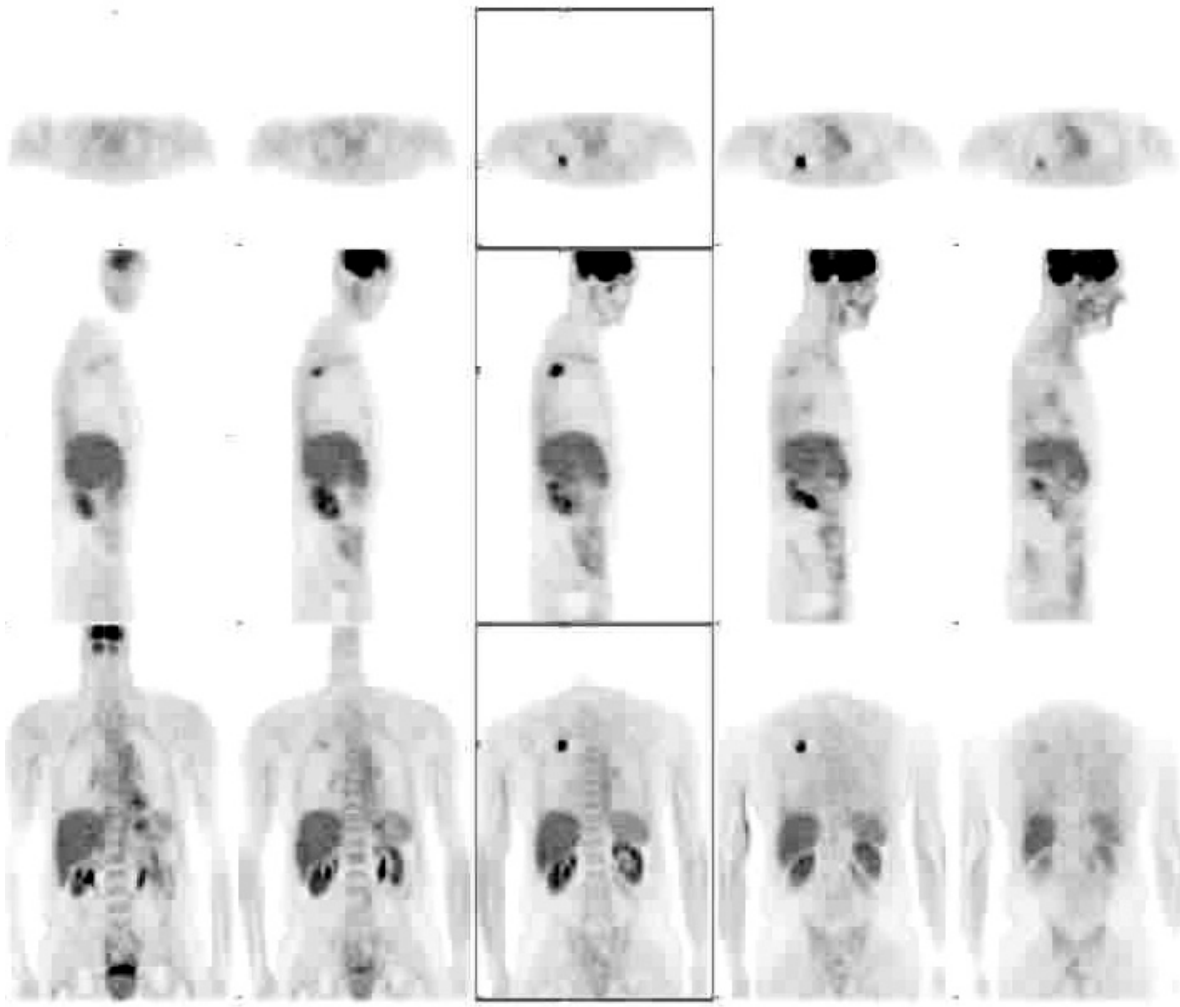

Figure 6 : After the injection of 16 mci IV of FDG, positron emission tomography images were obtained from the base of the skull to the proximal thigh. Transaxial, sagittal, and coronal images demonstrate a moderately sized area of hyperactivity at the superoposterior aspect of the right upper lobe. The standardized uptake value of this lesion is 6. Otherwise, there is no evidence of any abnormalities to suspect metastases in the mediastinum, retroperitoneum, abdomen, or pelvis.

Limitations of FDG-PET Imaging in CRC

As with any other imaging modality, FDG-PET has some limitations. FDG-PET imaging may fail to detect small volume disease due to partial-volume effect (volume averaging with limited system resolution) with small lesions under 1 cm or in necrotic lesions with only a thin rim of viable tissue. The sensitivity of FDG-PET for identification of mucinous-type CRC and its metastases is lower than that for the more common nonmucinous-type tumor. This is possibly due to the relative abundance of mucin and tumor hypocellularity (8,34). False-positive exams can also occur as physiologic and benign increased FDG uptake can mimic malignant disease. Normal urinary and gastrointestinal tract accumulation of the tracer may occasionally be difficult to differentiate from a malignant lesion (9).

Uptake at sites of prior anastamosis has also been described (8). This demonstrates the importance of correlating FDG uptake with clinical findings and results of conventional, anatomic imaging studies. Foci of FDG-PET accumulation should be evaluated with a CT scan through the region of abnormality to confirm the presence of a lesion and evaluate its resectability. Following radiation therapy, FDG accumulation may be related to radiation induced inflammation. However, by 6 months following radiotherapy, any activity noted on FDG-PET exams should be considered consistent with tumor recurrence (9).

Conclusion

Although FDG-PET cannot match the anatomic resolution of conventional imaging techniques, it is particularly useful for identification and characterization of hepatic and extrahepatic disease. FDG-PET can show foci of metastatic disease that may not be apparent on conventional anatomic imaging and can aid in the characterization of indeterminate soft tissue masses. FDG-PET is an invaluable modality due to its high specificity, particularly in postsurgical sites where other modalities cannot differentiate postsurgical changes from residual or recurrent malignancy. In addition, PET can detect unsuspected extrahepatic malignant lesions and, thus, alter surgical plans in a significant number of patients. FDG-PET should be considered as a complementary imaging technique that increases the specificity of structural imaging studies and also serves as a screening method for the entire body to detect and stage disease. The high accuracy of FDG-PET makes this a cost-effective nuclear medicine test for the workup of patients with CRC.

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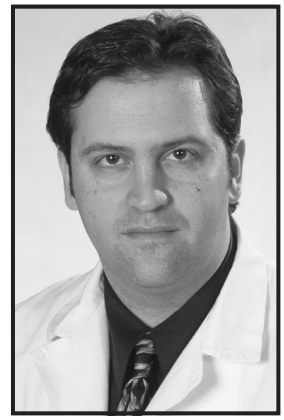

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