

## Chapter II.5

# Colorectal Cancer

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### Introduction

Colorectal cancer (CRC) is the third most common cause of malignancy in both men and women. The incidence rate has decreased over the last two decades partially due to an increase in screening. The American Cancer Society (ACS) estimates that there are approximately 149,000 new cases of CRC per year and approximately 50,000 patients per year die from this disease in the USA, representing 10% of new cases and 8% of all cancer deaths. Approximately 70–80% of patients are treated with curative intent, mostly by surgery. Chemotherapy alone, or in combination with radiation (for rectal cancer), is given before or after surgery to most patients whose tumor has penetrated the bowel wall or spread to lymph nodes. The overall survival at 1 and 5 years is 82 and 64%, respectively. The 5-year survival is 90% for localized stage, 68% when there is regional spread, and 10% when there are distant metastases.<sup>1</sup>

### <sup>18</sup>F-FDG PET and PET/CT for Screening and Diagnosis of Colorectal Carcinoma

The diagnosis of CRC is based on colonoscopy and biopsy. The ACS recommends yearly screening for CRC of asymptomatic individuals over the age of 50 with fecal occult blood test and flexible sigmoidoscopy every 5 years.<sup>2</sup>

In 2008, the American College of Radiology (ACR), the ACS, and the US Multisociety Task Force on CRC (composed of the three gastroenterology societies: the American Gastroenterology Association, American Society for Gastrointestinal Endoscopy, and American College of Gastroenterology) reviewed a broad range of screening modalities for CRC including various forms of stool tests, flexible sigmoidoscopy, colonoscopy, barium enema, and computed tomography (CT) colonography.<sup>3</sup> Examinations designed to both prevent and detect cancer are encouraged, and CT colonography (virtual colonoscopy) is one of the newly recommended screening tests.

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Although  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) is not routinely used for screening or diagnosing CRC, it is not uncommon to detect this malignancy incidentally on whole body studies performed for other indications.

$^{18}\text{F}$ -FDG uptake, which is normally present in the gastrointestinal tract, can occasionally be difficult to differentiate from a malignant lesion. Mild-to-moderate diffuse colonic uptake has been associated with a normal colonoscopy, segmental intense uptake can be due to colitis, and focal uptake can be associated with benign adenomas and premalignant and malignant lesions. Incidental detection of unexpected focal areas of  $^{18}\text{F}$ -FDG uptake located in the gastrointestinal tract, unlikely related to the known primary, is seen in 3–5% of patients. More than 50% of these unexpected lesions need further attention, including newly diagnosed asymptomatic CRC and tubular or villous adenomas and, less frequently, metastases. Therefore, in spite of  $^{18}\text{F}$ -FDG imaging not being recommended as a routine tool for detection or screening for precancerous or malignant colonic neoplasms, the identification of focal colon uptake should not be ignored.<sup>4–7</sup>

### **$^{18}\text{F}$ -FDG PET and PET/CT in the Initial Staging of Colorectal Carcinoma**

The preoperative staging with imaging modalities is usually limited because most patients will need to undergo colectomy to prevent intestinal obstruction and bleeding. The extent of the disease can be evaluated during surgery with excision of pericolic and mesenteric lymph nodes along with peritoneal exploration. Preoperative  $^{18}\text{F}$ -FDG imaging may be helpful in the detection of distant metastases and will cancel surgery in patients with increased surgical risk. It may also be helpful as a baseline evaluation prior to neoadjuvant chemotherapy in patients with advanced stage disease.  $^{18}\text{F}$ -FDG imaging is a powerful tool for assessment of the response to therapy.

### **$^{18}\text{F}$ -FDG PET and PET/CT for Assessment of Recurrent Colorectal Carcinoma**

#### ***Detection and Restaging of Recurrence***

Most CRCs are detected early and treated surgically with curative intent. A recent retrospective review of 1,838 patients who underwent curative resection of non-metastatic CRC with a minimum follow-up of 3 years reported an overall recurrence rate of 16.4%, with a local recurrence rate of 8.5%, with or without systemic metastases.<sup>8</sup>

For patients who present with isolated liver metastases, hepatic resection is the only curative therapy but has been associated with significant morbidity and mortality.<sup>9</sup> The poor prognosis of extrahepatic metastases is considered a contraindication to hepatic resection.<sup>10</sup> Therefore, accurate non-invasive detection of inoperable disease with imaging modalities plays a pivotal role in selecting patients who would benefit from surgery.

A number of studies have demonstrated the role of  $^{18}\text{F}$ -FDG PET as a metabolic imaging modality for detecting recurrent or metastatic CRC. Overall, the sensitivity of  $^{18}\text{F}$ -FDG PET is in the 90% range, with a specificity greater than 70%, both superior to CT. A meta-analysis of 11 clinical reports and 577 patients determined that the sensitivity and specificity of  $^{18}\text{F}$ -FDG PET for detecting recurrent CRC were 97 and 76%,

respectively.<sup>11</sup> A comprehensive review of the <sup>18</sup>F-FDG PET literature (including 2,244 patients) reported a weighted average sensitivity and specificity of 94 and 87%, respectively, compared to 79 and 73% for CT.<sup>12</sup> False-negative <sup>18</sup>F-FDG PET findings have been reported with mucinous adenocarcinoma.<sup>13,14</sup> The performance of <sup>18</sup>F-FDG PET for detection of hepatic and extrahepatic metastases, local recurrence, and relapsed disease in patients with rising carcinoembryonic antigen (CEA) levels and negative CT studies is discussed with the patient cases at the end of this chapter. The presence of extrahepatic disease has a significant effect on the management of these patients. <sup>18</sup>F-FDG PET is currently the most sensitive non-invasive modality to detect and localize extrahepatic disease in patients with CRC.<sup>15</sup>

Fused PET/CT images are especially important in the abdomen and pelvis, in order to clarify and precisely localize non-specific <sup>18</sup>F-FDG uptake to the stomach, small bowel and colon, and the urinary tract. In a study of 204 patients including 34 gastrointestinal tumors, investigators at Rambam Medical Center<sup>16</sup> concluded that PET/CT improved the diagnostic accuracy in approximately 50% of patients as compared to PET stand-alone. Fusion images improved characterization of equivocal lesions as either definitely benign in 10% or 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 impacted on the management of 14% of patients, including 20% of all patients in this study with gastrointestinal tumors. Changes in management of patients with CRC included guided colonoscopy with biopsy for local recurrence, guided biopsy to metastatic lymph nodes, guided surgery and referred patients to chemotherapy. Similar conclusions were found in a study of 173 patients performed at Vanderbilt University, including 24 with CRC.<sup>17</sup> In an additional study of 45 patients with CRC <sup>18</sup>F-FDG PET/CT increased the interpretation accuracy and certainty of lesion localization, decreasing the frequency of equivocal lesions by 50% as compared to PET alone, with a subsequent increase by 25% in the number of definite locations and in the overall correct staging from 78 to 89% of patients.<sup>18</sup>

Selznert et al.<sup>19</sup> have compared contrast-enhanced CT and non-enhanced PET/CT in 76 patients referred for restaging prior to resection of hepatic metastases. For detection of hepatic metastases, the two modalities had similar sensitivities of 95 and 91%, respectively. However, for evaluation of patients who had a prior hepatic resection, PET/CT had a specificity of 100% compared to only 50% for contrast-enhanced CT. For local recurrence and extrahepatic metastases, PET/CT demonstrated superior sensitivity (~90% range) compared to contrast-enhanced CT (50–60%). The performance of PET/contrast-enhanced CT has also been compared to PET/low-dose CT.<sup>20,21</sup> PET/low-dose CT was superior to stand-alone contrast-enhanced CT in 50% of patients by detection of additional metastases and change therapy in 10% of patients. PET/contrast-enhanced CT had a further incremental value to PET/low-dose CT in 72% of patients mainly by providing correct segmental localization of hepatic metastases and thus changing the management in 42% of patients. For nodal staging of patients with rectal cancer, the accuracy of PET/contrast-enhanced CT was slightly superior than that of PET/low-dose CT (79% versus 70%), with no statistical significance.

### ***Impact on Management and Cost Analysis in Patients with Recurrent Disease***

In a meta-analysis of the literature, <sup>18</sup>F-FDG PET imaging changed the management in 29% (102/349) of patients.<sup>11</sup> A comprehensive review of the <sup>18</sup>F-FDG PET literature has

reported a weighted average change of management related to  $^{18}\text{F}$ -FDG PET findings in 32% of 915 patients.<sup>12</sup>

In a survey-based study of 60 referring oncologists, surgeons, and generalists,  $^{18}\text{F}$ -FDG PET had a major impact on the management of CRC 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.<sup>22</sup>

In a 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  $^{18}\text{F}$ -FDG PET imaging, especially by detecting unsuspected extrahepatic disease.<sup>23</sup> A meta-analysis assessing the performance of  $^{18}\text{F}$ -FDG PET in patients with hepatic metastases demonstrated its higher specificity when compared to CT (96% versus 84%) for detection of hepatic metastases and higher sensitivity than CT (91% versus 61%) for detection of extrahepatic metastases.  $^{18}\text{F}$ -FDG PET changed the management of 31% of patients (range 20–58%).<sup>24</sup>  $^{18}\text{F}$ -FDG PET also improves prognostic stratification in patients with recurrent CRC.<sup>25</sup> In that study, two groups of symptomatic patients were studied: patients with a residual structural lesion suggestive of recurrent tumor and patients with potentially resectable pulmonary or hepatic metastases. Data were similar in both groups.  $^{18}\text{F}$ -FDG PET detected additional sites of disease in 48 and 44% of patients, and a change in planned management was documented in 66 and 49%, respectively. These management plans were implemented in 96% of patients. Follow-up data showed progressive disease in 60 and 66% of patients with additional lesions detected by  $^{18}\text{F}$ -FDG PET compared with conventional imaging, and in 36 and 39% of patients with no additional lesions detected by PET.

Although survival is not an endpoint for a diagnostic test, Strasberg et al.<sup>26</sup> have estimated the survival of patients who underwent  $^{18}\text{F}$ -FDG PET imaging in their preoperative evaluation for resection of hepatic metastases. The overall 3-year survival was 77%, with a lower confidence limit of 60%, higher than the range of 30–64% in previously published series. In patients undergoing  $^{18}\text{F}$ -FDG imaging prior to hepatic resection, the 3-year disease-free survival rate was 40%, again higher than that usually reported. This same group of investigators<sup>27</sup> recently reported the 5-year survival after resection of metastases from CRC. The 5-year survival rate was 30% by pooling the data of 19 studies with a total of 6,090 patients and appeared not to have changed over time. These results were compared to their group of 100 patients with hepatic metastases, who were preoperatively staged for resection with curative intent with the addition of  $^{18}\text{F}$ -FDG imaging. The 5-year survival rate improved to 58%, thus indicating the ability to define a subgroup of patients with a better prognosis. The main contribution was in detecting occult disease, leading to a reduction of futile surgeries.

Another study investigated the role of  $^{18}\text{F}$ -FDG PET in addition to conventional diagnostic methods compared to conventional diagnostic methods alone for selection of patients with metastatic CRC for surgery.<sup>28</sup> The percent of futile surgery was lower if  $^{18}\text{F}$ -FDG PET was included in the presurgical evaluation (19% versus 28%). However, for patients ultimately undergoing surgical treatment, the overall survival at 3 years was similar, 60% versus 51%.

Including  $^{18}\text{F}$ -FDG PET in the evaluation of patients with recurrent CRC has been shown to be cost-effective in studies using clinical evaluation of effectiveness with modeling of costs and studies using decision tree sensitivity analysis.<sup>29,30</sup>

## **<sup>18</sup>F-FDG Imaging for Monitoring Therapy Response of Colorectal Carcinoma**

### ***Systemic Chemotherapy***

<sup>18</sup>F-FDG imaging has an important role in monitoring patients with advanced stage CRC that is associated with poor prognosis. Systemic chemotherapy with 5-fluorouracil has demonstrated effective palliation and improved survival, although response rates are only 10–20% in patients with advanced disease.<sup>31</sup> More recently, chemotherapeutic agents such as irinotecan and oxiplatin have been shown to improve survival in combination with 5-fluorouracil-based therapies. In a study of 18 patients with hepatic metastases, Findley et al.<sup>32</sup> were able to discriminate responders from non-responders after 4–5 weeks of chemotherapy with fluorouracil by measuring <sup>18</sup>F-FDG uptake before and during therapy.

Several studies have compared detection of hepatic metastases in patients with and without preoperative adjuvant chemotherapy.<sup>33–36</sup> Both PET and CT were shown to have a lower sensitivity for detection of hepatic metastases after chemotherapy ranging from 49 to 62% for <sup>18</sup>F-FDG imaging compared to 65–92% for CT. CT is slightly more sensitive than <sup>18</sup>F-FDG especially for small lesions. Normalization of FDG uptake in hepatic metastases after chemotherapy was followed by complete histopathological response in only 15% of lesions.<sup>37</sup> Therefore, curative resection should not be deferred based on <sup>18</sup>F-FDG imaging.

### ***Radiation Therapy***

For patients with rectal carcinoma, systemic chemotherapy with 5-fluorouracil in combination with radiotherapy has been shown to improve survival. <sup>18</sup>F-FDG PET/CT fusion images have the potential to provide better maps than CT alone for field and dose modulation of radiation therapy, including for patients with CRC.<sup>38</sup>

After treatment of these patients, radiation-induced inflammation and necrosis make the differential diagnosis of post-radiation changes from residual tumor difficult with ultrasound, CT, and MRI.<sup>39</sup> Increased <sup>18</sup>F-FDG uptake immediately following radiation may be due to inflammatory changes and is not always associated with residual tumor. The time course of post-radiation <sup>18</sup>F-FDG activity has not been studied systematically. It is, however, generally accepted that increased <sup>18</sup>F-FDG activity at 6 months after completion of radiation therapy most likely represents tumor recurrence. A case-controlled study of 60 <sup>18</sup>F-FDG studies performed at 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.<sup>40</sup> In a study of 15 patients with locally advanced rectal carcinoma, Guillem et al.<sup>41</sup> demonstrated that <sup>18</sup>F-FDG imaging performed before and 4–5 weeks after completion of preoperative radiation and 5-fluorouracil-based chemotherapy had the potential to assess the pathological response. The same authors further demonstrated that <sup>18</sup>F-FDG imaging could predict long-term outcome after a median follow-up of 42 months.<sup>42</sup> The mean percent decrease in SUVmax was 69% for patients free from recurrence and 37% for patients with recurrence.

## ***Regional Therapy to the Liver***

Hepatic metastases can be treated with regional therapy to the liver. A variety of regional treatment modalities for hepatic metastases have been investigated, including chemotherapy administered through the hepatic artery using infusion pumps, selective chemoembolization, cryoablation, alcohol and radiofrequency ablation, and radioembolization using  $^{90}\text{Y}$ -microspheres.<sup>43</sup> Monitoring regional therapy to malignant hepatic lesions is discussed in Chapter II.7.

## **Summary**

Evaluation of patients with known or suspected recurrent CRC is now an accepted indication for  $^{18}\text{F}$ -FDG PET/CT, with complementary information provided by the PET and CT components of the study and unique, incremental information added by fused images. The most common indications for  $^{18}\text{F}$ -FDG PET/CT in patients with CRC are for diagnosis of recurrence and for preoperative N and M restaging of known recurrence considered to be resectable.  $^{18}\text{F}$ -FDG PET/CT is also of value for differentiation of post-treatment changes from recurrent tumor, differentiation of benign from malignant lesions such as indeterminate lymph nodes, hepatic and pulmonary lesions, and evaluation of patients with rising tumor markers and no other evidence of active malignancy. Addition of  $^{18}\text{F}$ -FDG PET/CT to the evaluation of these patients reduces overall treatment costs by accurately differentiating between patients who will benefit from surgical procedures from those who will not.

Although initial staging at the time of diagnosis is often performed during colectomy,  $^{18}\text{F}$ -FDG PET/CT is now commonly performed preoperatively. It is particularly useful if  $^{18}\text{F}$ -FDG PET shows metastases and unnecessary surgery can be avoided. Screening for recurrence in patients at high risk has also been advocated, as has been monitoring patient response to therapy. Both these clinical indications for  $^{18}\text{F}$ -FDG imaging in patients with CRC need further evaluation in large studies.

## **Guidelines and Recommendations for the Use of $^{18}\text{F}$ -FDG PET and PET/CT**

The National Comprehensive Cancer Network (NCCN) has incorporated  $^{18}\text{F}$ -FDG PET and PET/CT in its practice guidelines and management algorithms for a variety of malignancies including CRC.<sup>44</sup> The use of  $^{18}\text{F}$ -FDG PET (PET/CT where available) is recommended in the following clinical scenarios:

- (1) Initial staging if conventional imaging studies are equivocal for metastatic disease
- (2) Rising CEA levels or suspicious symptoms for occult recurrence unless other imaging tests are diagnostic
- (3) Restaging of recurrent CRC if curative resection is considered

$^{18}\text{F}$ -FDG PET is not indicated:

- (1) For restaging after non-surgical treatment of metastatic disease
- (2) For post-treatment surveillance

A multidisciplinary panel of experts assessed meta-analyses and systematic reviews published in the  $^{18}\text{F}$ -FDG PET literature before March 2006 and made recommendations for the use of  $^{18}\text{F}$ -FDG PET in oncology<sup>45</sup>:

- (1) The panel found little evidence to support the use of  $^{18}\text{F}$ -FDG PET for the diagnosis of CRC.
- (2)  $^{18}\text{F}$ -FDG PET should be used routinely in addition to conventional imaging in the preoperative diagnostic workup of patients with potentially resectable hepatic metastases from CRC.
- (3)  $^{18}\text{F}$ -FDG PET should be performed following the conventional workup, especially if CEA levels are increased and the results of this workup are negative. PET can also be used to differentiate between local relapse and postsurgical scars.



## Case Presentations

### *Case II.5.1(DICOM Images on DVD)*

#### History

This 81-year-old man presented with a recurrent fibrohistiocytoma of the right upper chest, recently biopsied. A chest radiograph revealed a right lower lobe mass. Biopsy demonstrated an adenocarcinoma. He was referred for preoperative assessment with  $^{18}\text{F}$ -FDG PET/CT (Fig. II.5.1A–D).

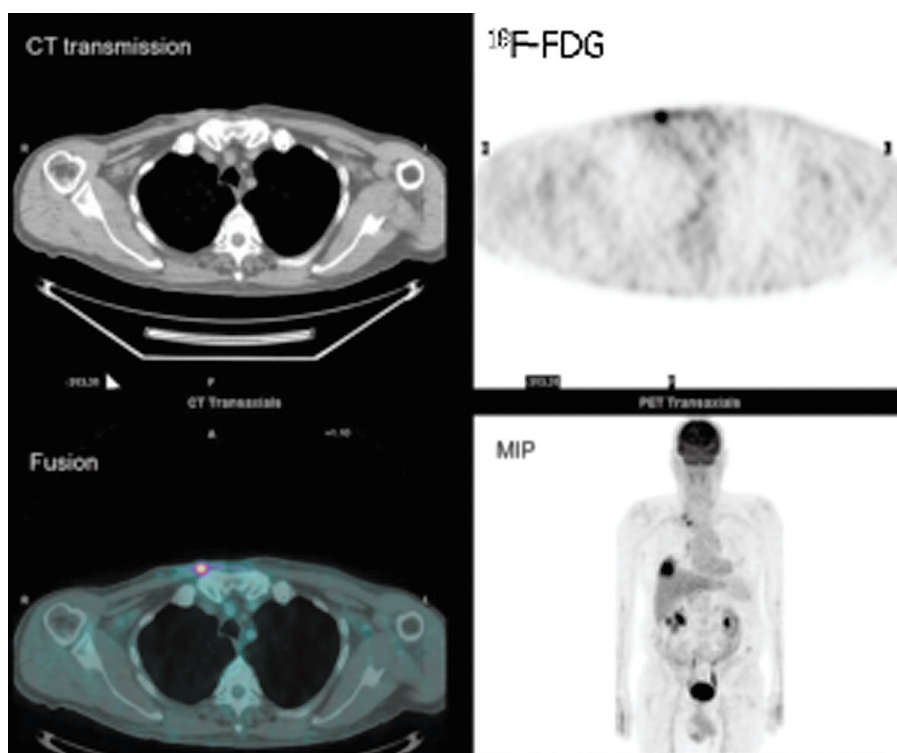


Fig. II.5.1A



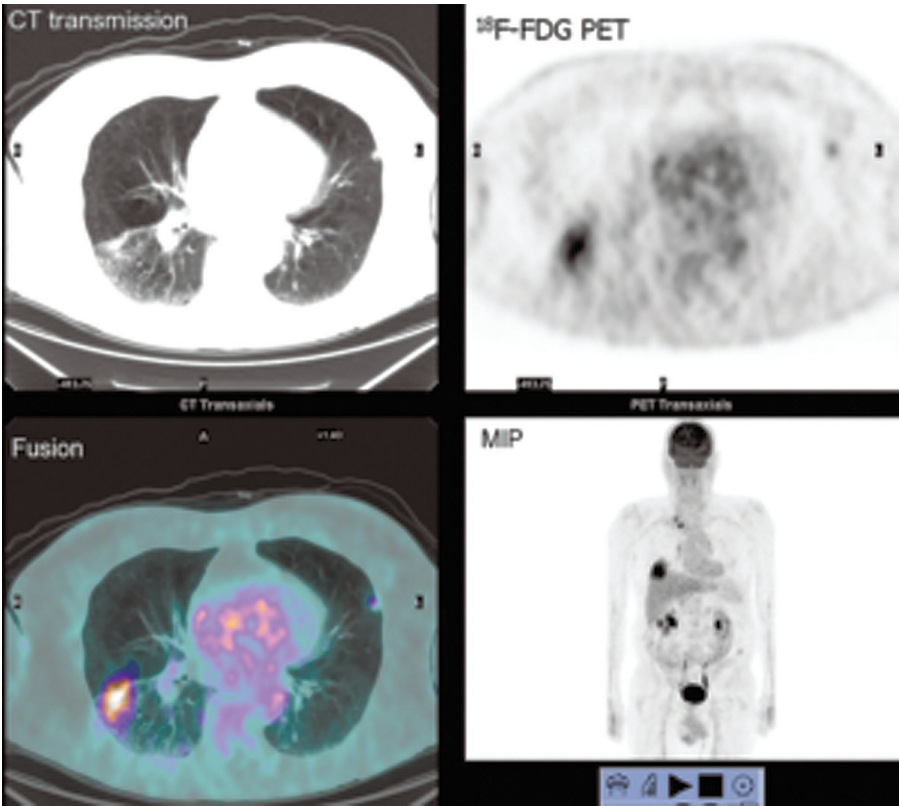


Fig. II.5.1B

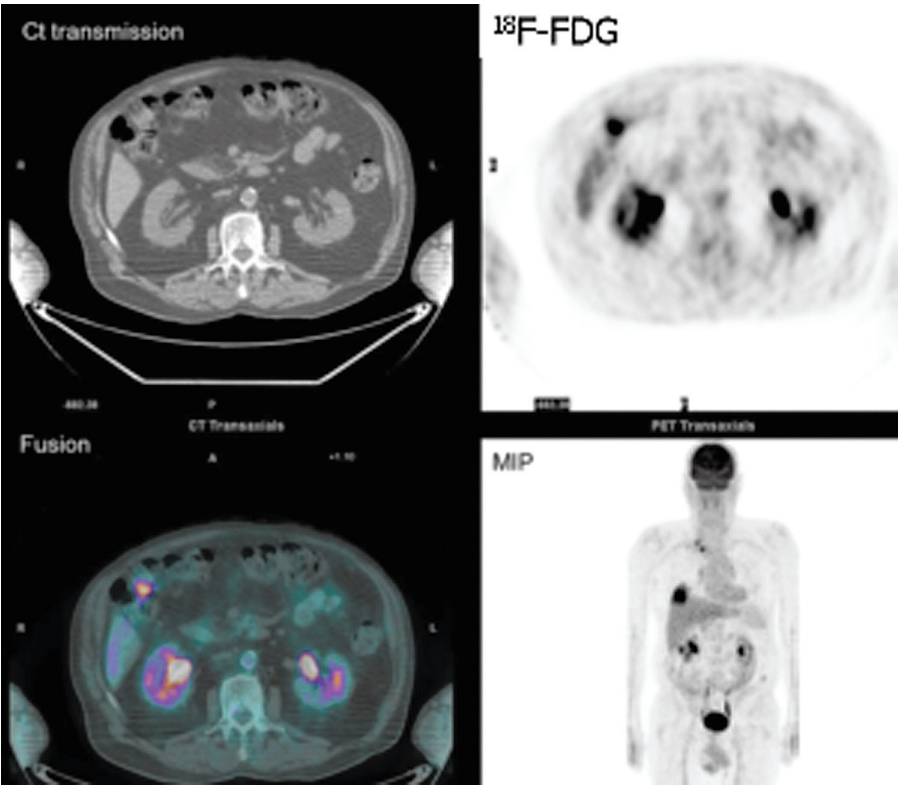


Fig. II.5.1C

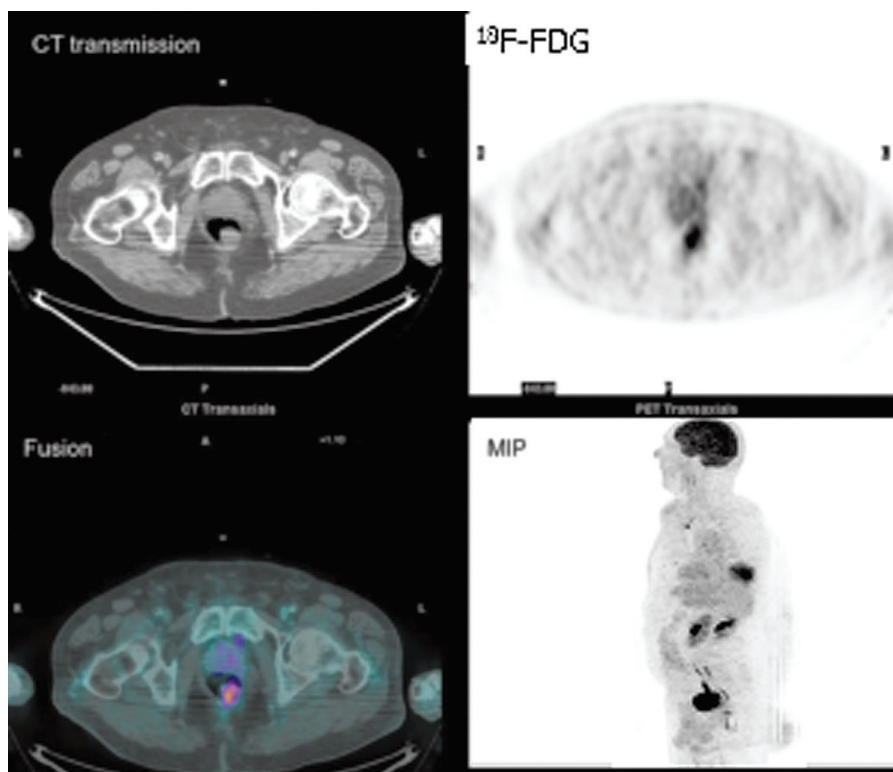


Fig. II.5.1D

### Findings

Two focal areas of intense  $^{18}\text{F}$ -FDG uptake in the anterior upper right hemithorax correspond to soft tissue stranding anterior to the proximal third of the right clavicle (Fig. II.5.1A). Given the patient's history of recurrent malignant fibrohistiocytoma in this region, these foci are consistent with local recurrence. A large focus of intense  $^{18}\text{F}$ -FDG uptake corresponding to a  $74 \times 41$  mm infiltrative mass is identified in the lateral aspect of the lower lobe of the right lung (maximum intensity projection [MIP] images). A 7 mm nodular density is present within the anterolateral aspect of the left upper lobe and demonstrates mild  $^{18}\text{F}$ -FDG uptake (Fig. II.5.1B). There is intense focal  $^{18}\text{F}$ -FDG uptake corresponding to an approximately 20 mm soft tissue mass within the transverse colon at the hepatic flexure (Fig. II.5.1C). An additional focus of mild-to-moderate  $^{18}\text{F}$ -FDG uptake corresponds to an exophytic lesion,  $20 \times 20$  mm in size, in the distal rectum (Fig. II.5.1D). Additional CT findings are seen on the DICOM images (DVD) and described in the clinical report.

### Discussion

These findings are consistent with the known recurrent malignant fibrohistiocytoma and right lower lobe adenocarcinoma. The 7 mm left lung nodule has mild uptake. It is at the size limit of PET resolution and suffers from partial volume averaging artifact being smaller than twice the resolution of the PET system. Any uptake in a structure less than twice the

resolution of the PET system is worrisome for malignancy. The degree and focality of uptake in the transverse colon and rectum are very concerning for a malignant or premalignant etiology. The patient underwent colonoscopy with biopsies. The lesion in the transverse colon was proven to represent moderately differentiated adenocarcinoma and the polyp resected from the rectum was a tubulovillous adenoma with high-grade dysplasia.

Agress and Cooper<sup>4</sup> reviewed <sup>18</sup>F-FDG PET studies of 1,750 patients with known or suspected malignancies. The authors found 58 unexpected focal areas of <sup>18</sup>F-FDG uptake unlikely to be related to the known primary tumor in 3.3% of patients. Forty-two lesions were pathologically confirmed: 71% were malignant or premalignant lesions, including adenoma and carcinoma of the colon. Similar data were published by Kamel and coworker who reviewed 3,281 patients,<sup>5</sup> Gutman et al. in 1,716 patients,<sup>6</sup> and Israel and coworkers in 4,390 patients.<sup>7</sup>

The sensitivity of <sup>18</sup>F-FDG imaging is highly dependent on both the size of the lesion, with up to 72% sensitivity for lesions greater than 10 mm in diameter, and the degree of dysplasia, reaching up to 89% for carcinoma and up to 76% for high-grade and 36% for low-grade degrees of dysplasia.<sup>46</sup> The sensitivity of <sup>18</sup>F-FDG imaging is lower for flat (sessile) premalignant lesions.<sup>47</sup>

## Diagnosis

1. Recurrent malignant fibrohistiocytoma.
2. Lung adenocarcinoma, right lower lobe.
3. Possible small metastasis in the left lung.
4. Transverse colon carcinoma.
5. Rectal high-grade tubular adenoma.

## Clinical Report: Body <sup>18</sup>F-FDG PET/CT (for DVD cases only)

### Indication

Initial staging of non-small cell lung carcinoma.

### History

The patient is an 81-year-old male with a history of recurrent fibrohistiocytoma of the right upper chest, which had been diagnosed 2 years earlier by excisional biopsy and followed by wide excision. The patient presented with a recurrent chest wall lesion, confirmed as recurrence at biopsy. A preoperative chest x-ray revealed a lung mass in the right lower lobe. Subsequent bronchoscopy with biopsy was consistent with adenocarcinoma, and the patient now presents for initial staging.

### Procedure

The fasting blood glucose level was 93 mg/dl. A dose of 480 MBq (13.0 mCi) of <sup>18</sup>F-FDG was administered intravenously in the right antecubital fossa. After a distribution time of 65 min, whole body low-dose CT without intravenous contrast was acquired to correct for attenuation and for anatomic localization, followed by PET images acquired over the head, neck, thorax, abdomen, and pelvis. The patient was positioned with the arms to the torso's sides.

## Findings

*Quality of the study:* The quality of this study is good.

*Head and neck:* There is physiologic distribution of the radiopharmaceutical in the brain and in the lymphoid and glandular tissues of the neck.

*Chest:* Two focal areas of intense  $^{18}\text{F}$ -FDG uptake correspond to soft tissue stranding immediately anterior to the proximal third of the right clavicle. Given the patient's history, these areas of uptake are most consistent with local recurrence of malignant fibrohistiocytoma. A large focus of intense  $^{18}\text{F}$ -FDG uptake corresponds to a  $74 \times 41$  mm infiltrative mass within the lateral aspect of the right lower lobe. A 7 mm nodular density is present within the anterolateral sub-pleural portion of the left upper lobe and demonstrates a mild degree of  $^{18}\text{F}$ -FDG uptake. Two sub-centimeter nodules are identified within the apex of the right lung on CT, below the PET resolution. There is mild pulmonary emphysema, old granulomatous disease in the mediastinum, and a small pericardial effusion.

*Abdomen and pelvis:* There is an area of focal, high-intensity  $^{18}\text{F}$ -FDG uptake corresponding to an approximately 20 mm soft tissue mass in the transverse colon at the level of the hepatic flexure. Another focus of mild-to-moderate degree of  $^{18}\text{F}$ -FDG uptake corresponds to an exophytic  $20 \times 20$  mm lesion within the distal rectum. There are multiple small gallstones and vascular calcifications in the aorta and its branches demonstrated on CT.

*Musculoskeletal:* There are degenerative changes in the spine.

## Impression

1. Intense  $^{18}\text{F}$ -FDG uptake in a right lower lobe mass, consistent with the known lung adenocarcinoma.
2. A small, 7 mm, nodular opacification within the anterolateral portion of the left upper lobe with mild  $^{18}\text{F}$ -FDG uptake, suggestive of metastasis.
3. Two sub-centimeter nodules in the apex of the right lung on CT, below the PET resolution.
4. Two focal areas of intense  $^{18}\text{F}$ -FDG uptake in soft tissue stranding anterior to the right clavicle, consistent with the known recurrent malignant fibrohistiocytoma.
5. Intense focal  $^{18}\text{F}$ -FDG uptake, corresponding to a 20 mm lesion in the transverse colon at the hepatic flexure and a focus of moderate uptake, corresponding to an exophytic 20 mm lesion in the distal rectum. The differential diagnosis includes malignancy versus benign polyp; correlation with colonoscopy is recommended.
6. Additional CT findings are described earlier.

### Case II.5.2

#### History

This 63-year-old male presented with anal carcinoma. A biopsy revealed a moderately differentiated adenocarcinoma. CT demonstrated a large lesion in the left lobe of the liver. The patient was referred to PET/CT for initial staging (Fig. II.5.2A–D).

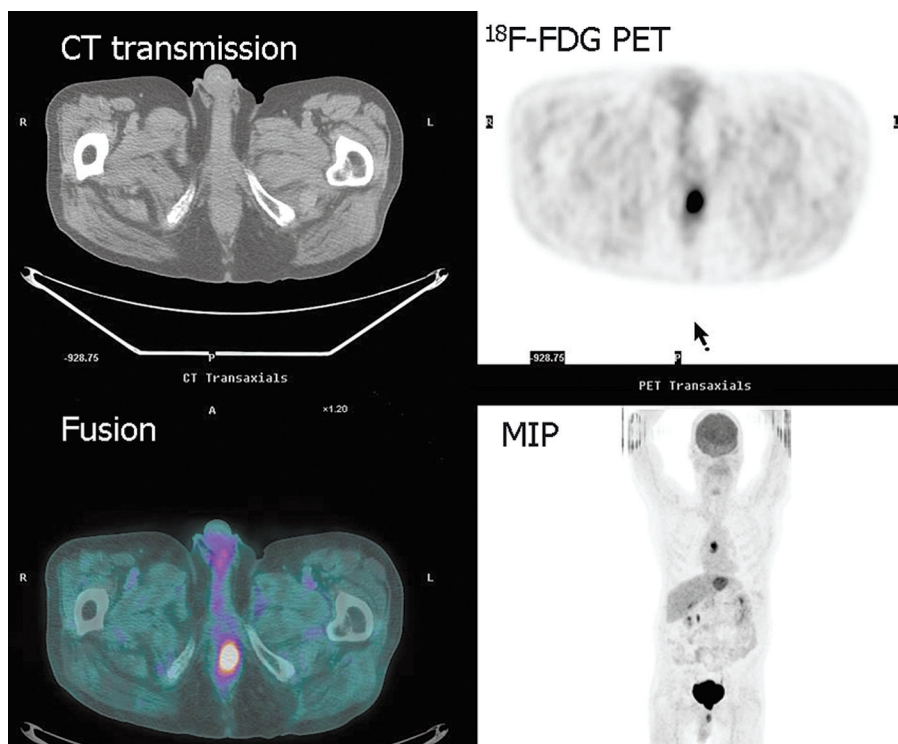


Fig. II.5.2A

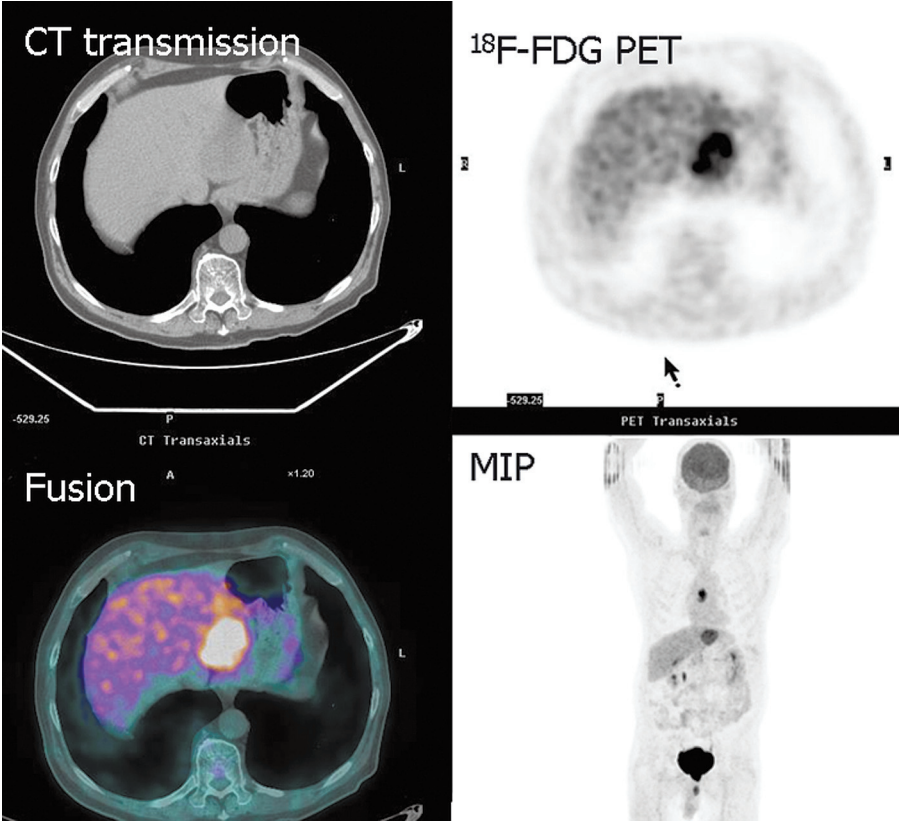


Fig. II.5.2B



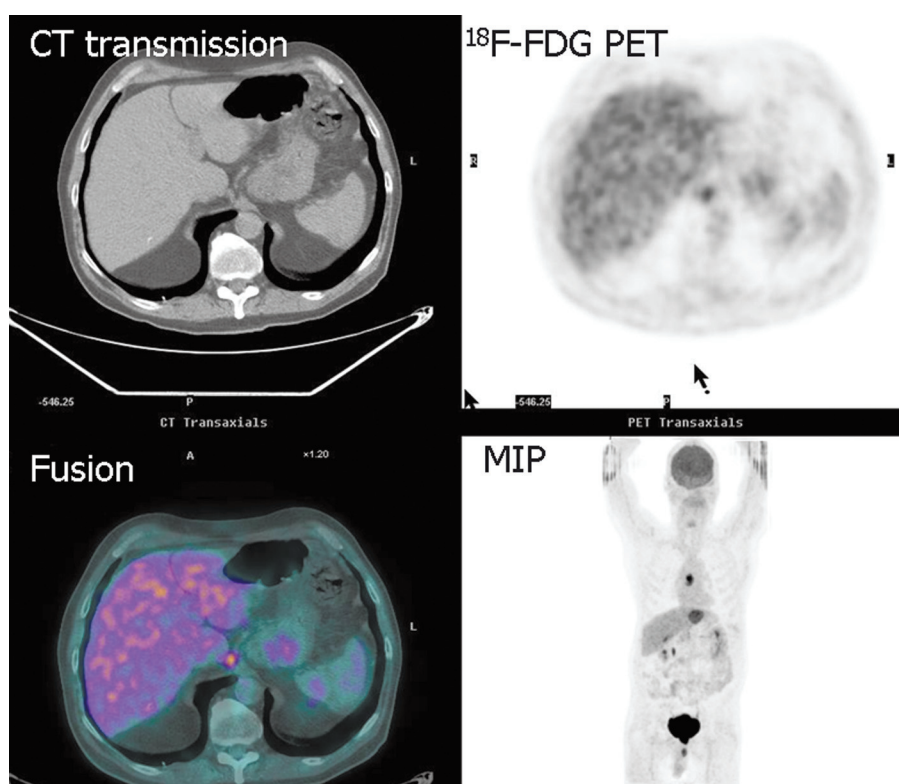


Fig. II.5.2C

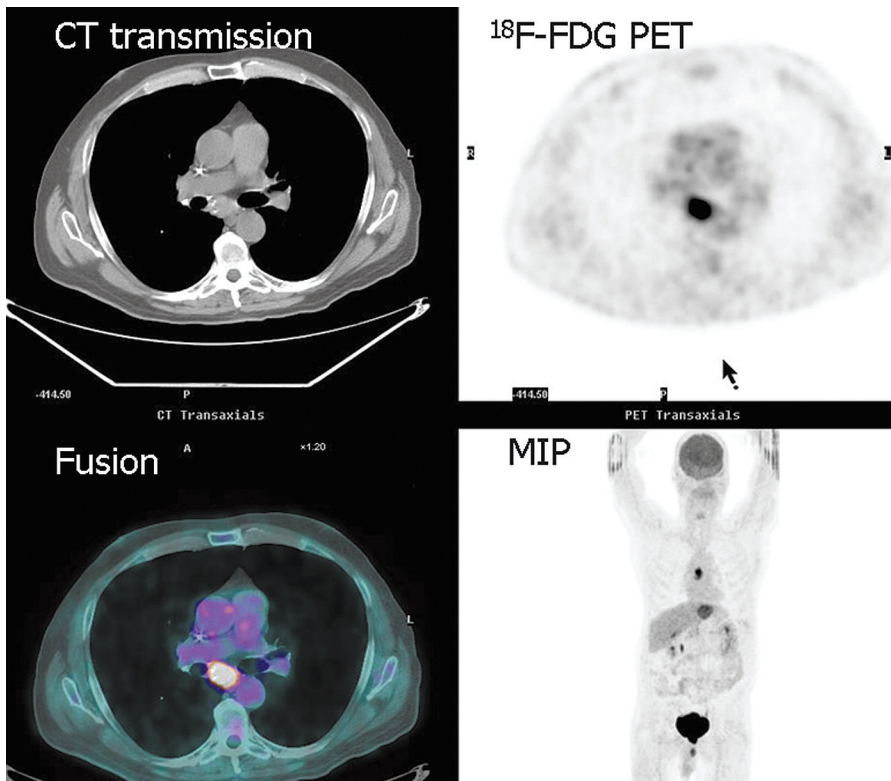


Fig. II.5.2D

### Findings

Focal intense  $^{18}\text{F}$ -FDG uptake is seen in the rectum corresponding to thickening of the anus, consistent with the known primary tumor (Fig. II.5.2A). There is a  $57 \times 47$  mm hypodense lesion in the left lobe of the liver seen on CT, which demonstrated intense  $^{18}\text{F}$ -FDG uptake, indicating a hepatic metastasis (Fig. II.5.2B). In addition, a small focus of uptake is seen in the right para-aortic/peri-esophageal region corresponding to a sub-centimeter lymph node retrospectively seen also on CT (Fig. II.5.2C) and a larger focus of uptake in the subcarinal mediastinum corresponding to a  $17 \times 25$  mm lymph node or nodal conglomerate (Fig. II.5.2D), each consistent with metastasis.

### Discussion

$^{18}\text{F}$ -FDG uptake in the anus represents the known primary tumor. As there was evidence of distant hepatic and extrahepatic metastases, surgical cure was not an option and the patient was referred for chemotherapy. PET/CT allowed precise localization of the distribution of extrahepatic disease, with the full extent of this disease seen on CT only in retrospect.

Several studies have evaluated the usefulness of  $^{18}\text{F}$ -FDG PET for staging patients with known or suspected primary CRC.  $^{18}\text{F}$ -FDG PET imaging identified almost all primary carcinomas. Both  $^{18}\text{F}$ -FDG and CT had equally low sensitivities for detection of loco-regional lymph node involvement, with a sensitivity of approximately 30% each. However,

<sup>18</sup>F-FDG PET was superior to CT for detection of hepatic metastases, with sensitivity and specificity greater than 90%, compared to 38 and 97%, respectively, for CT. <sup>18</sup>F-FDG PET changed the treatment modality in 8% of patients and the extent of surgery in 13%.<sup>48</sup> False-positive <sup>18</sup>F-FDG findings include abscesses, fistulas, diverticulitis, and adenomas.

**Diagnosis**

1. Primary rectal adenocarcinoma.
2. Hepatic metastasis in the left lobe.
3. Evidence of extrahepatic nodal metastases in the right para-aortic/distal peri-esophageal region and in the subcarinal mediastinum, seen on CT only in retrospect.

### Case II.5.3

#### History

This 74-year-old male was diagnosed with colon carcinoma 9 months earlier and subsequently treated with an ileocolic resection. He was referred to PET/CT for evaluation of a hepatic lesion detected on CT performed for restaging (Fig. II.5.3).

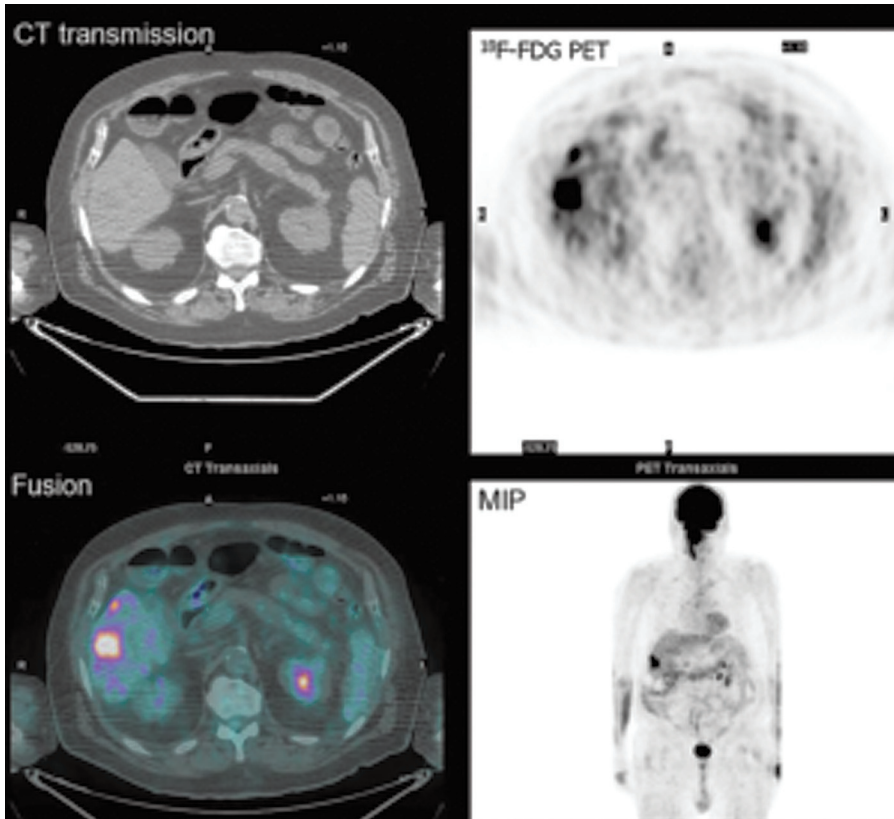


Fig. II.5.3

#### Findings

There is a focus of intense  $^{18}\text{F}$ -FDG uptake corresponding to a 25 mm hypodense lesion seen in the right lobe of the liver on CT. In addition, there is a second focus of intense  $^{18}\text{F}$ -FDG uptake anterior to the first lesion. There is physiological uptake in the glandular and lymphoid tissue of the neck and motion artifact of the head and neck region, best appreciated on the anterior maximum intensity projection (MIP) image. There is mild linear uptake along the sternum (seen on MIP), corresponding to a prior sternotomy and coronary artery bypass grafting evident on CT (not shown). There is no evidence of extra-hepatic metastases.

## Discussion

The findings are consistent with two hepatic metastases in segment 6 of the liver. In the absence of extrahepatic lesions, this patient is a candidate for resection. For patients who present with isolated liver metastases, hepatic resection is the only curative therapy, but this procedure is associated with significant morbidity and mortality.<sup>9</sup> The poor prognosis of extrahepatic metastases represents a contraindication to hepatic resection.<sup>10</sup> Therefore, accurate non-invasive detection of inoperable disease plays a pivotal role in selecting patients who would benefit from surgery.

A meta-analysis comparing non-invasive imaging methods (ultrasound [US], CT, MRI, and <sup>18</sup>F-FDG PET) for the detection of hepatic metastases from colorectal, gastric, and esophageal cancers demonstrated that, at an equivalent specificity of 85%, <sup>18</sup>F-FDG PET had the highest sensitivity (90%) compared to MRI (76%), CT (72%), and US (55%).<sup>49</sup> A subsequent meta-analysis, including studies that performed MRI with gadolinium and superparamagnetic iron oxide particle (SPIO) enhancement, came to similar conclusions for a patient-based analysis.<sup>50</sup> For a lesion-based analysis, <sup>18</sup>F-FDG PET had the highest sensitivity of 76% compared to 66% for unenhanced MRI and 64% for CT. Both gadolinium- and SPIO-enhanced MRI were superior to non-enhanced MRI. SPIO-MRI was the most sensitive technique, with a sensitivity of 90% for detection of lesions greater than 10 mm, compared to 76% for <sup>18</sup>F-FDG PET. In patients with CRC, the sensitivity of <sup>18</sup>F-FDG PET for detection of hepatic metastases was compared to that of multiphase CT, using intraoperative ultrasound as reference standard for lesions of different sizes.<sup>28</sup> The overall sensitivity was similar for PET (71%) and CT (72%); both modalities missed approximately 30% of smaller lesions but resulted in a change of management in 7% of patients. One study compared mangafodipir-trisodium-enhanced hepatic MRI with <sup>18</sup>F-FDG for detection of liver metastases in patients with colorectal and pancreatic cancer.<sup>51</sup> On a per-patient analysis, MRI and <sup>18</sup>F-FDG showed sensitivities of 97 and 93%, positive predictive values of 100 and 90%, and accuracies of 97 and 85%, respectively. On a per-lesion analysis, MRI and <sup>18</sup>F-FDG showed sensitivities of 81 and 67%, positive predictive values of 90 and 81%, and accuracies of 76 and 64%, respectively. <sup>18</sup>F-FDG imaging provided additional information regarding the presence of extrahepatic disease and was therefore useful in initial staging. However, significantly more and smaller (sub-centimeter) hepatic metastases were detected on MRI than on <sup>18</sup>F-FDG PET.

Valk et al.<sup>52</sup> compared the sensitivity and specificity of <sup>18</sup>F-FDG and CT for detection of metastases in specific anatomic locations and found that <sup>18</sup>F-FDG PET was more sensitive than CT in all locations except the lung, where the two modalities were equivalent. The greatest differences between PET and CT were found in the abdomen, pelvis, and retroperitoneum, where over one-third of PET-positive lesions were negative by CT. PET was more specific than CT in all locations except the retroperitoneum, but less significant than for the sensitivity.

In a prospective study of 51 patients prior to resection of hepatic metastases, clinical management decisions based on conventional diagnostic methods were changed in 20% of patients based on the findings of <sup>18</sup>F-FDG imaging, especially due to detection of unsuspected extrahepatic disease.<sup>23</sup>

## Diagnosis

1. Two hepatic metastases.
2. No evidence of extrahepatic disease.

**Case II.5.4 (DICOM Images on DVD)**

**History**

This 69-year-old male has a history of sigmoid colon carcinoma treated with sigmoidectomy 2 years earlier. One year later, he had tumor recurrence in the liver and underwent resection of the left hepatic lobe. At surgery metastatic lymph nodes were found, and lymph node dissection was also performed. The patient then received chemotherapy and was referred to  $^{18}\text{F}$ -FDG PET/CT for restaging (Fig. II.5.4A–C). Figure II.5.4C is not corrected for attenuation correction (no AC).

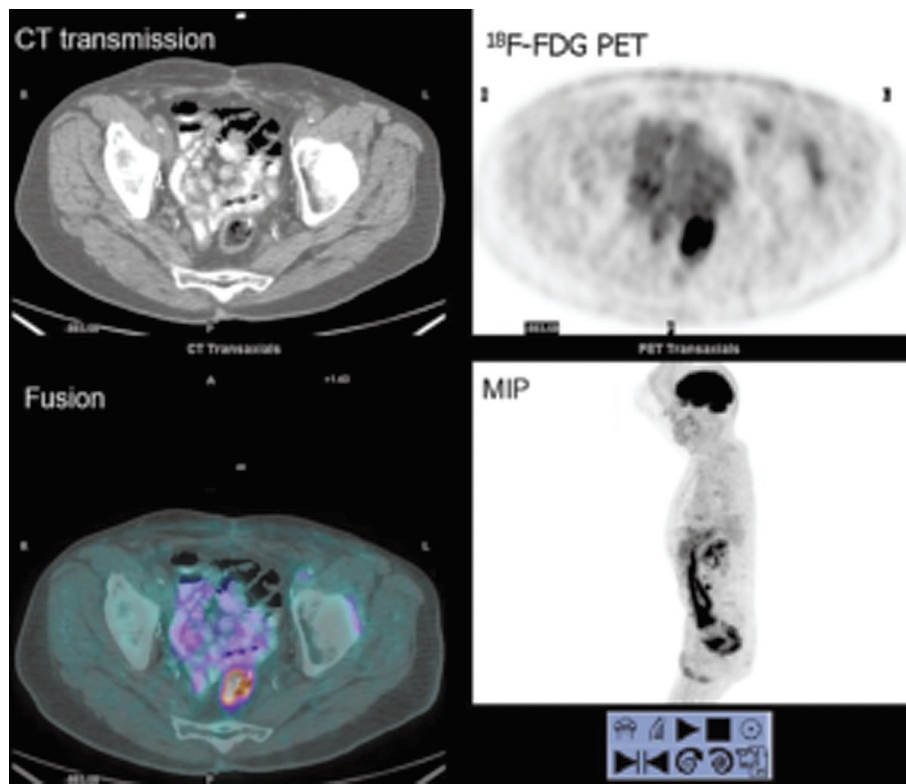


Fig. II.5.4A



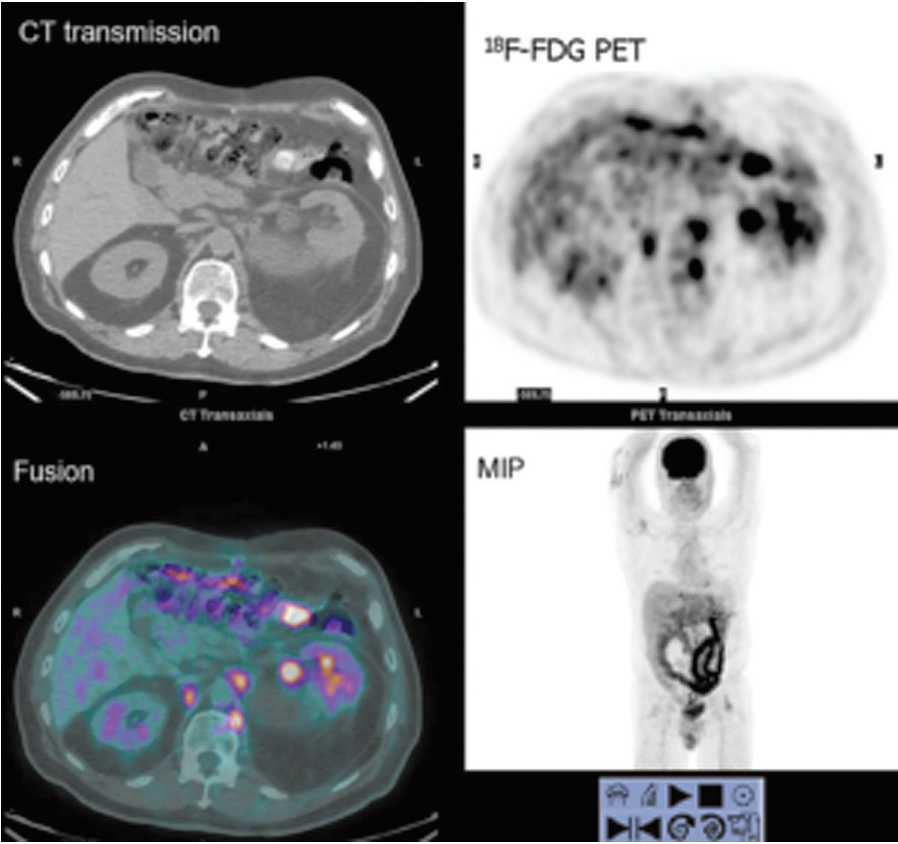


Fig. II.5.4B



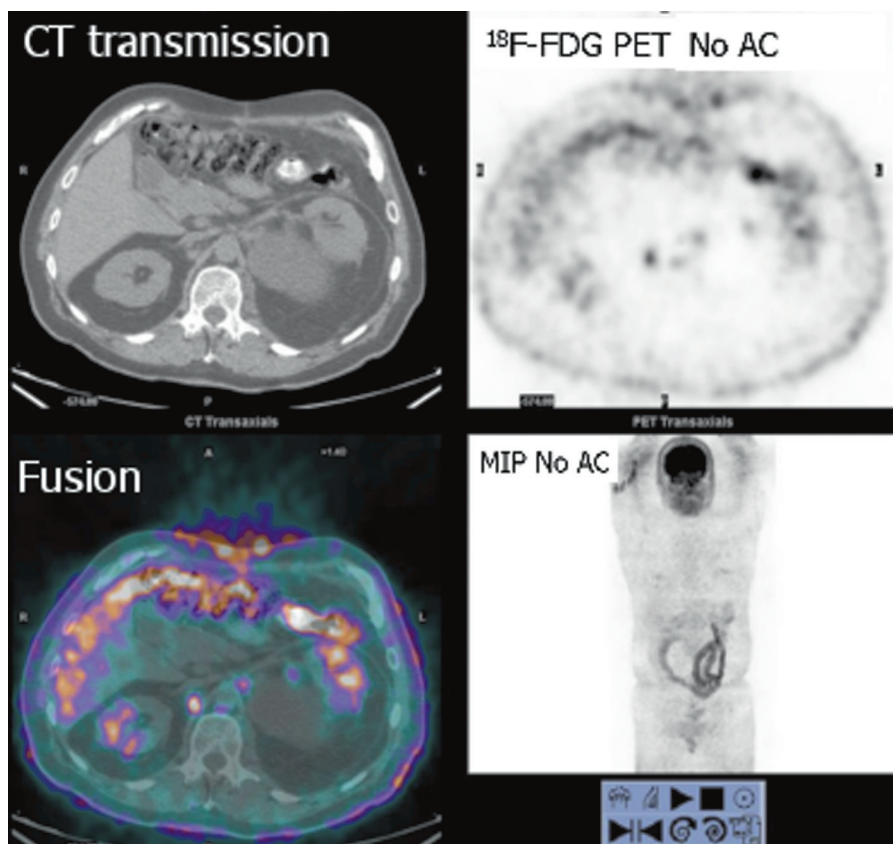


Fig. II.5.4C

### Findings

There is a focus of intense  $^{18}\text{F}$ -FDG uptake corresponding to the surgical anastomosis in the sigmoid colon (Fig. II.5.4A). The anastomosis can be identified on CT by the presence of staples. There are also three foci of uptake corresponding to sub-centimeter lymph nodes on CT in the left retrocrural, left para-aortic, and right retrocaval regions.

There is intense uptake throughout much of the GI tract, seen on both the attenuation corrected (Fig. II.5.4B) and the non-attenuation corrected (Fig. II.5.4C) images.

Examination of the CT component of the study (see DICOM images on the DVD) reveals a 12 cm fluid collection on the left, felt to represent a post-surgical lymphocele, resulting in displacement of the left kidney anteriorly and in mild hydronephrosis. There is an exophytic left renal cyst.

### Discussion

The findings indicate local recurrence and metastatic disease in superior retroperitoneal lymph nodes. Since the patient was no longer a candidate for surgery with curative intent, he was referred to further chemotherapy.

Several studies have compared  $^{18}\text{F}$ -FDG PET and CT for detection of local recurrence. CT was equivocal in most cases, whereas the accuracy of  $^{18}\text{F}$ -FDG PET imaging exceeded 90%. In the largest study including 76 patients comparing  $^{18}\text{F}$ -FDG PET and CT for differentiation of scar from local recurrence, the accuracy was 95 and 65%, respectively.<sup>53</sup> In addition,  $^{18}\text{F}$ -FDG detected metastases in normal size lymph nodes seen on CT. PET/CT improved retrospective detection of lesions on both the PET and the CT images and improved their accurate characterization as either benign or malignant. PET/CT also allowed more precise anatomic localization of the  $^{18}\text{F}$ -FDG-avid foci. In this case study, sub-centimeter retroperitoneal lymph nodes were retrospectively identified on CT after being characterized as malignant by PET because of their  $^{18}\text{F}$ -FDG avidity.  $^{18}\text{F}$ -FDG uptake in the sigmoid colon could be precisely localized to the region of the anastomosis, therefore characterized as malignant since the surgical insult was remote.

Diffuse bowel uptake is also seen in this patient. The uptake is intense and fairly homogeneous, and seen on both the attenuation corrected (AC) and the non-attenuation corrected (non-AC) images. The major differential diagnosis for diffuse bowel uptake includes normal variation, malignancy such as peritoneal carcinomatosis with diffuse bowel wall tumor implant, ischemic gut, diverticulitis, inflammatory bowel disease, and enterocolitis, especially in the context of myeloablative chemotherapy in association with bone marrow transplantation. The presence of GI contrast can, at times, produce an AC artifact from a combination of “over-correction” and peristalsis occurring in the interim between the CT and the PET acquisition of the images. This can result in misregistration between the two components of the PET/CT. If the uptake in the bowel is also seen on the non-AC image, as in this case, the GI contrast given for the diagnostic CT is not the source for artefactual GI tract uptake on PET/CT. In this case, the most likely cause for the bowel uptake was enterocolitis.

## Diagnosis

1. Local recurrence at the surgical anastomosis.
2. Metastases to retroperitoneal lymph nodes.

## Clinical Report: Body $^{18}\text{F}$ -FDG PET/CT (for DVD cases only)

### Indication

Restaging of colon cancer.

### History

This 69-year-old male with a history of adenocarcinoma in the sigmoid colon, status post-sigmoidectomy 2 years earlier followed by chemotherapy, was found to have recurrent metastatic disease to the liver, treated with left hepatic resection. At surgery, metastatic lymph nodes were found, and the patient also underwent lymph node dissection. The patient then received additional chemotherapy and is now referred for restaging by  $^{18}\text{F}$ -FDG PET/CT.

### Procedure

The patient is to receive a diagnostic, contrast-enhanced CT study of the chest, abdomen, and pelvis immediately after the PET/CT scan and, therefore, oral contrast was

administered prior to  $^{18}\text{F}$ -FDG administration. The fasting blood glucose level was 85 mg/dl at the time of injection of the radioisotope; 470 MBq (12.8 mCi) of  $^{18}\text{F}$ -FDG was administered intravenously via the right antecubital vein. After a distribution time of 90 min, a whole body low-dose CT without IV contrast was acquired for attenuation correction and for anatomic localization, followed by PET imaging over the brain, neck, thorax, abdomen, and pelvis. The patient was positioned with his arms above the head.

## Findings

*Quality of the study:* The quality of the study is good.

*Head and neck:* There is physiologic distribution of  $^{18}\text{F}$ -FDG in the cortex of the brain and in the glandular and lymphoid tissue of the neck.

*Chest:* There is physiologic uptake in the myocardium. The lungs are clear.

*Abdomen and pelvis:* There are several foci of intense  $^{18}\text{F}$ -FDG uptake within multiple retroperitoneal lymph nodes. Two of these lymph nodes are at the level of the mid-pole of the right kidney. Four lymph nodes are located in the left periaortic region at the same level and caudal to it. The largest lymph node is located caudally anterior to the left renal vein and measures  $14 \times 9$  mm. There is a large  $127 \times 107$  mm fluid collection that is not  $^{18}\text{F}$ -FDG avid on the left, which most likely represents a postsurgical lymphocele. This lesion has resulted in displacement of the left kidney anteriorly and in subsequent mild left hydronephrosis.

An exophytic left renal cyst is noted. There is intense  $^{18}\text{F}$ -FDG uptake corresponding to the anastomotic site in the sigmoid colon. There is also increased  $^{18}\text{F}$ -FDG uptake along the lateral margin of the distal sigmoid colon. In addition, there appears to be some wall thickening associated with intense  $^{18}\text{F}$ -FDG uptake within the rectum.

*Musculoskeletal:* There is a small amount of  $^{18}\text{F}$ -FDG uptake seen within the muscles of the right shoulder, which is likely inflammatory in etiology. Mild degenerative changes are seen throughout the spine with no abnormal  $^{18}\text{F}$ -FDG uptake.

## Impression

1. Increased  $^{18}\text{F}$ -FDG uptake at the site of the previous sigmoid anastomosis and along the lateral margin of the distal sigmoid. In addition, there is bowel wall thickening and  $^{18}\text{F}$ -FDG uptake in the rectum, consistent with residual viable malignant disease.
2. Multiple borderline-sized periaortic and retroperitoneal  $^{18}\text{F}$ -FDG-avid lymph nodes consistent with metastases.
3. Large fluid collection in the left perinephric space, suggesting a postsurgical lymphocele. This has resulted in anterior displacement of the left kidney and mild hydronephrosis.
4. For additional anatomic detail, refer to the report of the diagnostic, contrast-enhanced CT examinations of the chest, abdomen, and pelvis performed on the same day as the PET/CT.
5. Incidental findings include (a) surgical changes from a partial left hepatectomy, recto-sigmoid surgery, and prostatectomy; (b) stable scarring in the left lower lobe; and (c) left subclavian venous infusion port in place.

### Case II.5.5

#### History

This 56-year-old patient has a history of rectal carcinoma treated with surgical resection. He presented with rising CEA levels. CT of the abdomen and pelvis was negative. The patient was referred for  $^{18}\text{F}$ -FDG PET/CT imaging (Fig. II.5.5).

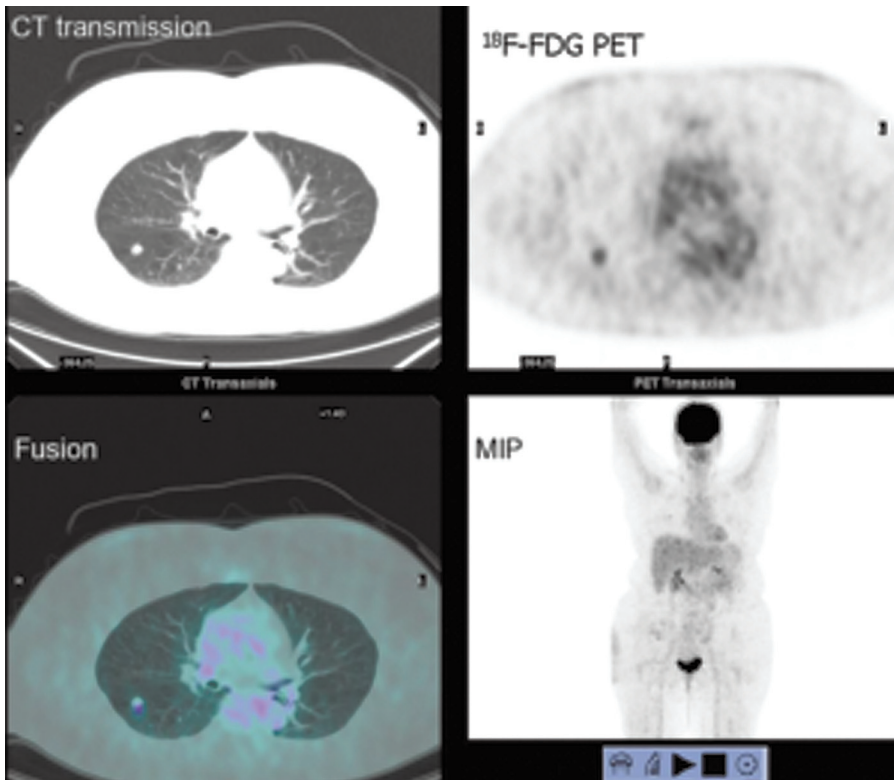


Fig. II.5.5

#### Findings

There is a focus of moderate  $^{18}\text{F}$ -FDG uptake corresponding to an 8 mm nodule in the lower lobe of the right lung. No additional foci of abnormal uptake are seen (Fig. II.5.5).

#### Discussion

$^{18}\text{F}$ -FDG uptake in this sub-centimeter lung nodule is suspicious for metastasis in a patient with a history of rectal carcinoma. Biopsy was recommended and confirmed the diagnosis. This example illustrates the value of PET/CT as a whole body imaging technique, allowing detection of metastases in unsuspected locations that are not always imaged with conventional workup.

The measurement of serum levels of CEA may be used to monitor patients for recurrence with a sensitivity of 59% and specificity of 84%. However, an elevated CEA level does not localize recurrent tumor. Flanagan et al.<sup>55</sup> reported the use of <sup>18</sup>F-FDG PET in 22 patients with unexplained elevation of serum CEA levels after resection of colorectal carcinoma, with no abnormal findings on conventional workup, including CT. Sensitivity and specificity of <sup>18</sup>F-FDG PET for detection of tumor recurrence were 100 and 71%, respectively. Valk et al.<sup>52</sup> reported a 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. Pooled data from published studies demonstrate that <sup>18</sup>F-FDG PET detects tumor in 84% of patients with rising CEA levels and a negative conventional workup. Surgical resection is possible in 26% of these patients.

**Diagnosis**

Pulmonary metastasis in the right lower lobe.

### Case II.5.6

#### History

A 38-year-old male diagnosed with colon cancer 1 year previously presented with rising serum CEA levels. A recent CT demonstrated several large hypodense lesions in the liver. The patient was referred for  $^{18}\text{F}$ -FDG PET/CT prior to considering surgery (Fig. II.5.6).

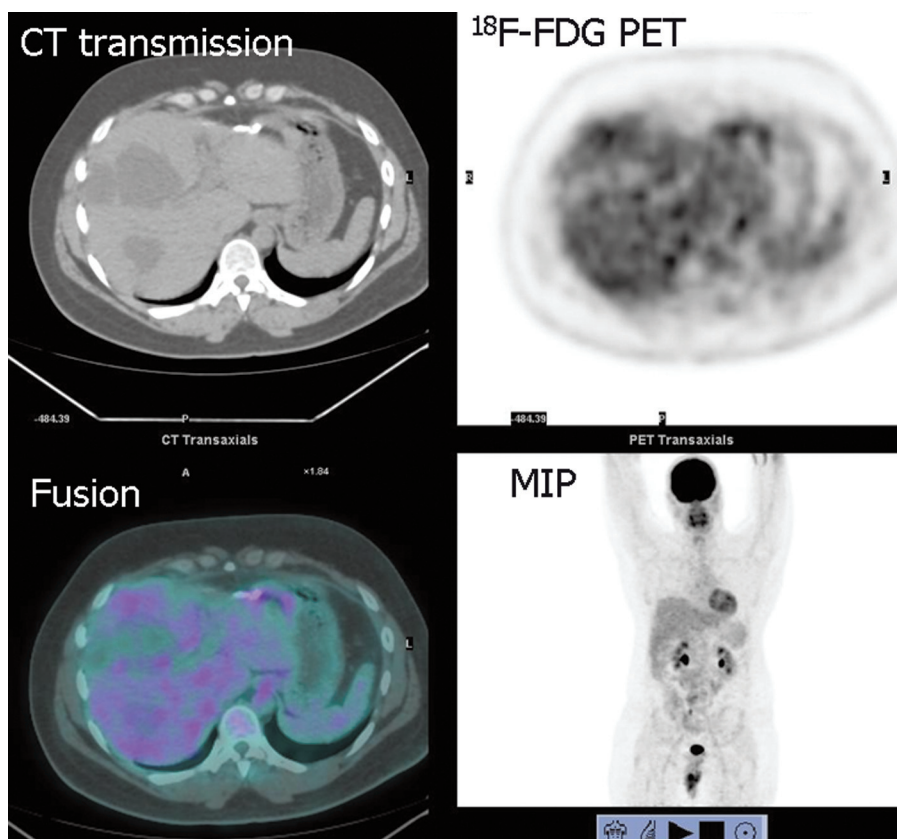


Fig. II.5.6

#### Findings

CT shows several large hypodense lesions in the right lobe of the liver, with no corresponding abnormal  $^{18}\text{F}$ -FDG uptake (Fig. II.5.6).

#### Discussion

The CT abnormalities are greater than 1 cm in diameter, therefore well within the resolution of PET, and yet do not demonstrate increased  $^{18}\text{F}$ -FDG uptake. When there is discordance between compelling laboratory and CT evidence for metastases and negative PET findings,

it is essential to review the histological features of the tumor. Biopsy of the liver revealed metastatic mucinous adenocarcinoma with signet ring features. Adenocarcinoma from various primary sources can have large mucinous components, as was the case in this patient, and can be false negative on  $^{18}\text{F}$ -FDG PET. The patient underwent partial right hepatectomy. This study also demonstrates the complementary nature of PET/CT; in this example, metastases were seen on CT but not on PET.

A meta-analysis of 11 clinical reports determined that the sensitivity and specificity for  $^{18}\text{F}$ -FDG PET for detection of recurrent CRC are 97 and 76%, respectively. These values are superior to that of CT, which has a sensitivity and specificity of 86 and 58%, respectively, for detection of extrahepatic recurrence.<sup>11</sup> However, false-negative  $^{18}\text{F}$ -FDG studies have been reported with mucinous adenocarcinoma. Whiteford et al.<sup>13</sup> reported that the sensitivity of  $^{18}\text{F}$ -FDG PET for detection of mucinous adenocarcinoma is significantly lower than for non-mucinous adenocarcinoma, 58 and 92%, respectively. These investigators also reported that  $^{18}\text{F}$ -FDG PET detected tumor in 60% (15/25) of patients with mucinous carcinoma (11 colorectal, 8 gastroesophageal, 2 pancreatic, 3 lung, and 1 breast) and postulated that the low sensitivity of  $^{18}\text{F}$ -FDG PET for detection of mucinous adenocarcinoma might be due to the relative hypocellularity of these tumors. Similar low sensitivity of 41% has been reported in a subsequent series of 22 patients.<sup>14</sup>

## Diagnosis

Mucinous adenocarcinoma metastatic to the liver seen on CT but not on  $^{18}\text{F}$ -FDG PET.



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