The Role and Limitations of 18-Fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG-PET) Scan and Computerized Tomography (CT) in Restaging Patients with Hepatic Colorectal Metastases Following Neoadjuvant Chemotherapy: Comparison with Operative and Pathological Findings

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Abstract

Background Recent data confirmed the importance of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the selection of patients with colorectal hepatic metastases for surgery. Neoadjuvant chemotherapy before hepatic resection in selected cases may improve outcome. The influence of chemotherapy on the sensitivity of FDG-PET and CT in detecting liver metastases is not known.

Methods Patients were assigned to either neoadjuvant treatment or immediate hepatic resection according to resectability, risk of recurrence, extrahepatic disease, and patient preference. Two-thirds of them underwent FDG-PET/CT before chemotherapy; all underwent preoperative contrast-enhanced CT and FDG-PET/CT. Those without extensive extrahepatic disease underwent open exploration and resection of all the metastases according to original imaging findings. Operative and pathological findings were compared to imaging results.

Results Twenty-seven patients (33 lesions) underwent immediate hepatic resection (group 1), and 48 patients (122 lesions) received preoperative neoadjuvant chemotherapy (group 2). Sensitivity of FDG-PET and CT in detecting colorectal (CR) metastases was significantly higher in group 1 than in group 2 (FDG-PET: 93.3 vs 49%, $P < 0.0001$; CT: 87.5 vs 65.3, $P = 0.038$). CT had a higher sensitivity than FDG-PET in detecting CR metastases following neoadjuvant therapy (65.3 vs 49%,

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$P<0.0001$). Sensitivity of FDG-PET, but not of CT, was lower in group 2 patients whose chemotherapy included bevacizumab compared to patients who did not receive bevacizumab (39 vs 59%, $P=0.068$).

Conclusions FDG-PET/CT sensitivity is lowered by neoadjuvant chemotherapy. CT is more sensitive than FDG-PET in detecting CR metastases following neoadjuvant therapy. Surgical decision-making requires information from multiple imaging modalities and pretreatment findings. Baseline FDG-PET and CT before neoadjuvant therapy are mandatory.

Keywords Colorectal liver metastases · FDG-PET · Neoadjuvant chemotherapy

Introduction

The liver is the most common, and often the only, site of distant metastases from colorectal cancer (CRC).[1] Hepatic resection is the only effective therapy for a subset of patients with CRC metastatic to the liver, and is associated with 5-year survival rates ranging from 25 to 40%.[2–5] From 60 to 65% of patients will, however, develop recurrent tumors after hepatic resection, indicating that they had harbored unrecognized intra- or extrahepatic tumor foci at the time of liver resection.[6] Moreover, several studies report unresectable disease in 40–70% of patients that undergo laparotomy for liver resection.[2,7,8] These data indicate that better patient selection is needed to avoid unnecessary operations. There are several potential ways of improving patient selection, one of which is the administration of neoadjuvant therapy followed by reevaluation and better preoperative staging.

Positron emission tomography with the glucose analog 18-fluoro-2-deoxy-D-glucose (FDG-PET) is a sensitive diagnostic tool for the detection of colorectal metastases. Approximately 25% of patients are discovered to have new intra- or extrahepatic tumors on FDG-PET performed after standard imaging.[9–13] Screening with FDG-PET before hepatic resection for CRC significantly improves the survival rates of resected patients, probably by improving patient selection.[14]

The role of neoadjuvant chemotherapy to down-stage nonresectable liver metastases and to improve outcome following hepatic resection of resectable liver metastases is an evolving concept, but one that is not yet established. With the recent application of new chemotherapeutic agents, such as irinotecan, oxaliplatin, and bevacizumab, improved response rates can be achieved and the use of these agents in the neoadjuvant setting would appear to be especially relevant for patients with nonresectable disease or patients with high risk of recurrence.[15–18]

The aim of our study was to examine the effect of neoadjuvant chemotherapy for hepatic colorectal metastases on CT and FDG-PET/CT findings and to define the role of these imaging techniques in this setting. To do so, we compared CT and FDG-PET/CT findings with histopathological reports.

Patients and Methods

Patients

Patients with colorectal liver metastases were assigned to receive either an immediate liver resection (group 1) or neoadjuvant chemotherapy (group 2). The criteria for neoadjuvant treatment were:

1. Nonresectable tumors due to size, location, and number and assessment of the surgical team that complete (R0) resection was not technically possible.
2. High risk of recurrence according to the Memorial Sloan–Kettering Cancer Center (MSKCC) clinical risk score to assess risk of recurrence.[19] Specifically, patients with two or more risk factors [number of metastases >1, disease-free survival <12 months, carcinoembryonic antigen (CEA) levels >200 ng/ml, metastases from the colonic tumor to regional lymph nodes, size of the largest metastases >5 cm] were assigned to neoadjuvant treatment.
3. Presence of extrahepatic disease.
4. Oncologist's preference—this applied to patients with MSKCC >2 that were referred from other hospitals for immediate surgery. The decision not to administer neoadjuvant therapy was not necessarily in agreement with our policy.
5. Patient's preference—patients who refused neoadjuvant therapy were assigned to immediate surgery when feasible.

Neoadjuvant Chemotherapy

Treatment consisted of a neoadjuvant chemotherapeutic combination of 5-fluorouracil, leucovorin, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Seventeen patients (35%) were also given bevacizumab. Most of the group 2 patients were given neoadjuvant irinotecan unless they were enrolled on a multicenter study whose protocol consisted of the administration of neoadjuvant oxaliplatin.

Staging

Before undergoing neoadjuvant chemotherapy, all group 2 patients underwent a triphasic contrast-enhanced CT scan, and a FDG-PET/CT was performed in 30 (62.5%) of them. All 75 patients in group 1 and group 2 underwent FDG-PET/CT and abdominal CT before liver surgery. The time interval between the last course of chemotherapy and the FDG-PET/CT scan

was at least 2 weeks, and surgical exploration took place within 1 month following the FDG-PET/CT scan in most of the cases. Because we used an integrated PET/CT technique, precise anatomical localization could be achieved and confirmed with the standard triphasic abdominal CT findings.

PET/CT

The patients were asked to fast for at least 4 h before undergoing PET/CT. Earlier lab tests had shown that they all had glucose levels <150 mg%. The patients received an intravenous injection of 370–666 MBq (10–18 mCi) of ^{18}F-FDG. Data acquisitions by an integrated PET/CT system (Discovery LS; GE Medical Systems, Milwaukee, WI, USA) were performed within 60–120 min after injection. Iodinated oral contrast material was given to opacify loops of the bowel on the CT image. Data acquisition was as follows: CT scanning was performed first, from the head to the pelvic floor, with 140 kV, 80 mA, a tube rotation time of 0.5 s, a pitch of 6, and a 5-mm section thickness, which was matched to the PET section thickness. Immediately after CT scanning, a PET emission scan that covered the identical transverse field of view was obtained. Acquisition time was 5 min per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation (Xeleris, Elgems, Haifa, Israel).

Studies of all patients were retrieved and read in consensus by two experts (U.M. and E.E.-S.). All suspected sites of metastatic disease showing an increased FDG uptake were recorded. The location of hepatic lesions was recorded according to the Couinaud segmental classification.

Hepatectomy

All patients without extensive extrahepatic disease underwent surgical exploration and intraoperative ultrasound (IOUS). Resections of all metastatic sites were performed by either anatomic or R0 nonanatomic resection, with a tendency toward maximal parenchymal preservation with nonanatomic resections.

Complete radiological response to neoadjuvant chemotherapy was defined as the complete resolution of all metastatic sites according to the CT and PET-CT. In these cases, careful palpation and IOUS were performed in search of remaining tumor or scarring. When there was no evidence of either, the tumor sites were resected according to the findings on the original imaging (i.e., before any response to neoadjuvant treatment).

Detection of Hepatic Metastases

To define the sensitivity of CT and FDG-PET/CT for liver metastases, imaging results were compared with the

presence and size of liver lesions as demonstrated and measured by histopathological reports.

Results

Patients

Between June 2002 and September 2005, 75 patients with 155 suspected metastatic lesions from a primary CRC underwent hepatic resection in our department. Group 1 included 27 patients with 33 lesions who underwent immediate liver resection and group 2 included 48 patients with 122 lesions who first received neoadjuvant chemotherapy before subsequently undergoing liver resection. The patient's profiles are outlined in Table 1. Table 2 lists the operative procedures that were performed in the two groups.

Detection of Hepatic Metastases

The overall findings, the sensitivity, specificity, and accuracy of triphasic contrast-enhanced CT and FDG-PET/CT in the detection of viable liver metastases compared to the pathological results are presented in Table 3. FDG-PET and CT had a statistically significant higher sensitivity in detecting liver metastases in patients who did not receive chemotherapy compared to patients who received chemotherapy (Table 3). Statistical analysis also revealed that triphasic contrast-enhanced CT had a

Table 1 Study Patients' Profiles

	Group 1 (n=27)	Group 2 (n=48)	P value
Sex ratio (F/M)	0.50	0.92	0.22
Mean age, years (std deviation)	66 (9.8)	61.25 (10.9)	0.06
Site			
Colon	9 (71%)	32 (66%)	0.74
Rectum	8 (29%)	16 (33%)	
LN metastases (Duke's >B in colonic specimen)	81.5%	82%	0.73
No. of liver tumors (mean) (std deviation)	1.19 (0.4)	2.52 (1.9)	0.0001
Max tumor diameter (largest) (std deviation)	3.53 cm (2.84)	3.9 cm (1.84)	0.49
Extrahepatic disease (no. of patients)	7	9	0.56
Prior liver resection	4	6	1
Mean MSKCC risk score (range)	1.82 (0–4)	2.48 (2–5)	0.003

Group 1, immediate hepatic resection; Group 2, hepatic resection following neoadjuvant chemotherapy
LN=lymph node

Table 2 Operative Procedures

Operative procedure (no. of patients; lesions)	Group 1 ($n=27$)	Group 2 ($n=48$)
Right hepatic lobectomy	5	8
Left hepatic lobectomy	4	4
Central hepatectomy	0	3
Right trisegmentectomy	1	0
Nonanatomic resections	15	29
Left lat segmentectomy	2	2
Explorative laparotomy (no resection)	0	2

Group 1, immediate hepatic resection; Group 2, hepatic resection following neoadjuvant chemotherapy

higher sensitivity than PET/CT in detecting colorectal metastasis following neoadjuvant treatment (65.3 vs 49%, respectively, $P<0.0001$), but not in patients who did not receive neoadjuvant therapy (87.5 vs 93.3%, $P=0.625$).

Four of the six false-positive (FP) results on FDG-PET involved patients who had previously undergone hepatic resection. These lesions were discovered on follow-up FDG-PET/CT. Uptake was observed along the resection site, and these patients underwent nonanatomic liver resections for suspected locally recurrent lesions. Pathologic evaluation failed to reveal any tumor cells. The positive predictive value of FDG-PET/CT for metastasis recurrence in the resection site was only 33%, and specificity was 60%.

Sensitivity of FDG-PET in the detection of colorectal metastasis correlated with the size of the metastasis (Table 4). Average size of the metastases in the two groups

Table 3 FDG-PET and CT—Comparison With Pathological Results

	Group 1 $n=33$	Group 2 $n=122$	P value
PET			
TP	29	48	
True negative (complete response)	–	20	
FP	2	4	
FN	2	50	
Sensitivity	93.3%	49%	<0.0001
Specificity	–	83.3%	
CT			
TP	28	64	
True negative (complete response)	–	18	
FP	1	6	
FN	4	34	
Sensitivity	87.5%	65.3%	0.038
Specificity	–	75%	

Group 1, immediate hepatic resection; group 2, hepatic resection following neoadjuvant chemotherapy

was 33.9 mm (standard deviation 19) in group 1 and 18.9 mm (standard deviation 19) in group 2, $P<0.0001$.

We also compared the sensitivity of CT and FDG-PET for patients who received FOLFIRI or FOLFOX ($n=31$) with patients who received the same regimen plus bevacizumab ($n=17$). The results are outlined in Table 5. We found that the sensitivity of FDG-PET, but not of CT, was lower in patients who received bevacizumab, although the difference did not reach statistical significance.

Detection of Extrahepatic Metastases

In group 1, there were one FP result for extrahepatic disease (suspected recurrence in colonic anastomosis, abdominal wall), one true-positive (TP) result (recurrence in mesocolic lymph nodes), and one false negative (FN) result (in a patient with peritoneal metastases). In group 2, there was one FP result (for suspected peritoneal metastasis), three TP results (recurrence in paraaortic lymph nodes and solitary lung metastasis), and two FN results (for peritoneal metastases).

Discussion

The role of neoadjuvant chemotherapy followed by hepatectomy for colorectal liver metastases has not yet been clearly established. New chemotherapeutic agents, including irinotecan, oxaliplatin, and the biologic agent bevacizumab, have yielded improved response rates in the treatment of advanced CRC. These agents may have a potential role in the neoadjuvant setting for down-staging both nonresectable disease to resectability[15,16] and resectable disease, probably mostly for patients with high risk of recurrence.[17] Our policy is to administer neoadjuvant treatment to patients with nonresectable disease, those with extrahepatic disease, and those with resectable disease who have two or more risk factors according to the MSKCC clinical risk score.[19] One of the theoretical benefits of neoadjuvant treatment is that patients who develop additional extrahepatic or intrahepatic metastases during this time period are spared a futile major operative procedure. Accurate staging before the beginning of neoadjuvant treatment and restaging following the treatment are crucial for optimal patient selection.

The standard preoperative staging of patients with colorectal liver metastases includes combined abdominal CT and chest x-ray or chest CT. It was recently demonstrated that FDG-PET as a complementary staging method improves the therapeutic management of patients with colorectal liver metastases.[20] Preoperative screening with FDG-PET results in an increased survival rate of patients who undergo liver resection.[14] This can be explained by the

Table 4 Sensitivity of FDG-PET: Correlation With Tumor Size

Tumor size	<1 cm	1–3 cm	>3 cm
Group 1 sensitivity	33%	100%	92%
(total no. of lesions)	(n=3)	(n=15)	(n=13)
Group 2 sensitivity	17%	78%	100%
(total no. of lesions)	(n=35)	(n=41)	(n=22)

Group 1, immediate hepatic resection; group 2, hepatic resection following neoadjuvant chemotherapy

detection of occult intra- and extrahepatic metastatic disease, thus obviating futile explorations. In the current study, the sensitivity of FDG-PET/CT following neoadjuvant therapy was only 49% compared to a sensitivity of 93.3% in patients who did not receive neoadjuvant treatment ($P<0.0001$). The influence of the chemotherapeutic drugs on the sensitivity of FDG-PET in detecting extrahepatic metastases is not known, but we could assume that it is influenced in a similar way. This may result in a higher-than-expected rate of nonresectable disease discovered at the time of laparotomy and more extrahepatic recurrences following resection. In our series, only three of the 48 patients (6.25%) who received neoadjuvant chemotherapy were found to have nonresectable disease (one had diffuse liver metastases and two had peritoneal spread) that was not discovered preoperatively by either abdominal CT or FDG-PET/CT. We believe that one of the reasons for the high operability rate is the fact that a significant number of patients underwent a baseline FDG-PET/CT before the administration of neoadjuvant chemotherapy. We therefore recommend performing a baseline FDG-PET scan for all candidates for liver resection before the administration of

Table 5 FDG-PET and CT in Patients who Received Chemotherapy With or Without Bevacizumab: Comparison With Pathological Results

	Bevacizumab −	Bevacizumab +	P value
PET			
TP	29	19	
True negative (complete response)	17	3	
FP	2	2	
FN	20	30	
Sensitivity	59%	39%	0.068
CT			
TP	33	31	
True negative (complete response)	13	5	
FP	6	0	
FN	16	18	
Sensitivity	67%	63%	0.9

neoadjuvant treatment. A longer follow-up is needed to assess the results of our application of this protocol.

The decreased sensitivity of FDG-PET/CT in detecting liver metastases should also be a consideration when planning the extent of liver resection. We believe that the extent of resection should be guided by additional imaging modalities, including abdominal CT and IOUS, in patients who received neoadjuvant treatment. In our series, triphasic contrast-enhanced abdominal CT had a higher sensitivity than FDG-PET/CT in detecting colorectal metastasis in patients who received neoadjuvant chemotherapy (65.3 vs 49%, $P<0.0001$). The higher sensitivity of CT alone compared to FDG-PET/CT in detecting small colorectal metastasis has been reported by Ruers et al.,[20] and this may be even greater in patients who received chemotherapy. An attractive solution is the integrated PET/CT scanner on which a diagnostic triphasic abdominal CT scan can be performed at the same setting as the PET scan.

There are several possible explanations for the decreased sensitivity of FDG-PET/CT in the detection of colorectal metastases following neoadjuvant therapy:

1. Size of the lesion. The sensitivity of FDG-PET in detecting colorectal metastasis was reported as being directly related to the size of the lesions.[20] We found similar results in our series (Table 4). The average size of the metastases following neoadjuvant treatment was significantly smaller than that in patients who did not receive chemotherapy (33.9 mm in group 1 and 18.9 mm in group 2, $P<0.0001$). Two FN results in group 1 and 32 in group 2 involved tumors smaller than 1 cm. We can assume that one of the main reasons for the decreased sensitivity of FDG-PET following chemotherapy is the decrease in size of the metastases.

2. Chemotherapy and "metabolic shutdown." It has been demonstrated that the sensitivity of FDG-PET is diminished in cancer patients who undergo the examination less than 2 weeks following the administration of chemotherapy,[21] presumably due to a temporary metabolic "shutdown." Although the scans in our study were done with a minimal interval of 2 weeks from the last course of chemotherapy, partial response to therapy may have caused decreased FDG uptake in metastatic lesions, making them undetectable in comparison to the physiological background uptake of FDG in the liver. This may have been a contributing factor to the FN results in our series. We found a lower sensitivity of FDG-PET (but not of CT) in detecting liver metastases following regimens including bevacizumab compared to regimens that did not include bevacizumab, although the difference did not reach statistical significance. This result may have significant clinical implications; however, it needs to be verified in larger series.

3. Time interval between the FDG-PET and surgery. In our series, two patients with FN results (two hepatic lesions) underwent surgery more than 2 months after FDG-PET was performed. Viable tumors were discovered at the site of the original metastases which had disappeared on FDG-PET following neoadjuvant treatment. Although it is conceivable that the relatively long interval between FDG-PET and surgery may have contributed to the FN results, we believe that these tumors may have been FN due the small size of the lesions following partial pathological response to chemotherapy.

4. Nonavid tumors. PET avidity of the tumors can be assessed only in patients who undergo a baseline FDG-PET before neoadjuvant treatment. It has been reported that FDG-PET is less sensitive for mucinous adenocarcinoma.[22] In our series, ten FN results (lesions) were in patients with nonavid mucinous adenocarcinoma (sensitivity 37.5%).

There were two FP results in group 1 and four FP results in group 2. Four of the six FP results were in patients who had undergone a previous hepatic resection, for which follow-up FDG-PET detected uptake in the same location of the resected metastasis. These patients underwent nonanatomic resections of the "lesions." The pathological examination revealed only foreign body reaction without any tumor cells. In our current study, FDG uptake in the tumor bed following previous resection had a positive predictive value of 33% (2/6). The specificity of FDG uptake in the tumor bed for recurrence was 60%. We believe that FDG uptake in the tumor bed following a previous liver resection is not specific for tumor recurrence, especially if the CEA levels are normal. Nguyen et al. demonstrated that FDG uptake may be high in various granulomatous lesions,[23] possibly explaining the FP results along resection margins. Therefore, biopsy or follow-up should be considered in these cases.

Conclusions

The sensitivity of FDG-PET in detecting colorectal hepatic metastases decreases significantly following neoadjuvant chemotherapy. This may result in a higher-than-expected rate of nonresectable disease discovered at the time of laparotomy and in more extrahepatic recurrences following resection. We recommend staging patients with a "baseline" contrast-enhanced FDG-PET/CT both before and after the administration of neoadjuvant therapy. The extent of hepatic resection should be guided by systematic integration of data from all additional imaging modalities (abdominal CT, IOUS), as well as by the original imaging findings (before the neoadjuvant treatment). We recommend resection of all metastases that achieved complete radiological response, whenever technically possible. Longer follow-up and further studies are required to justify neoadjuvant treatment and screening with FDG-PET/CT in patients with colorectal metastases to the liver who are at high risk of recurrence.

References

1. Kemeny N, Fong Y. Treatment of liver metastases. Cancer Medicine. Baltimore: Williams and Wilkins, 1997, pp 1939–1954.
2. Fortner JG, Silva JS, Golbey RB, et al. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. 1. Treatment by hepatic resection. Ann Surg 1984;199:306–316.
3. Adson MA, Van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colorectal cancer. Arch Surg 1984;11:647–651.
4. Hughes KS, Simon R, Soughourabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi institutional study of patterns of recurrence. Surgery 1986;100:278–284.
5. Scheele J, Strangl R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. World J Surg 1985;19:59–71.
6. Scheele J, Strangl R, Altendorf-Hofmann A, et al. Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 1991;11:13–29.
7. Gibbs JF, Weber TK, Rodriguez-Bigas MA, et al. Intraoperative determinants of unresectability for patients with colorectal hepatic metastases. Cancer 1982;82:1244–1249.
8. Steele G, Bleday R, Mayer RJ. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: gastrointestinal tumor study group protocol 6584. J Clin Oncol 1991;9:1105–1112.
9. Valk PE, Abella-Columna E, Haesman MK, et al. Whole body PET imaging with [18F]fluorodeoxyglucose in management of recurrent colorectal cancer. Arch Surg 1999;134:503–511.
10. Delbeke D, Vitola JV, Sandler MP, et al. Staging recurrent metastatic colorectal carcinoma with PET. J Nucl Med 1997;38:1196–1201.
11. Abdel-Nabi H, Doerr RJ, Lamonica DM, et al. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole body PET: correlation with histopathologic and CT findings. Radiology 1998;206:755–760.
12. Vitola JV, Delbeke D, Sandler MP, et al. PET to stage suspected metastatic colorectal carcinoma to the liver. Am J Surg 1996;171:21–26.
13. Flamen P, Stroobants S, Van-Cutsem E, et al. Additional value of whole-body PET with fluorine-18-2fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894–901.
14. Fernandez F, Drebin JA, Linehan DC, et al. Five year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with 18-f fluorodeoxyglucose (FDG-PET). Ann Surg 2004;240:438–450.
15. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastasis from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509–522.

16. Adam R. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases. Ann Oncol 2003;14 (Suppl 2):ii13–ii16.

17. Tanaka K, Adam R, Shimada H, et al. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. Br J Surg 2003;90:963–969.

18. Allen PJ, Kemeny N, Jarnagin W, et al. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. J Gastrointest Surg 2003;7:109–117.

19. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer. Ann Surg 1999;230:309–321.

20. Ruers TJM, Langenhoff BS, Neelman N, et al. Value of positron emission tomography with [f-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002;20:388–395.

21. Kostakoglu L, Goldsmith SJ. 18F-FDG PET evaluation of the response to therapy for lymphoma and for breast, lung, and colorectal carcinoma. J Nucl Med 2003;44:224–239.

22. Whitford MH, Yee LF, Ogunbiyi OA, et al. Usefulness of FDG-PET scan in the assessment of suspected metastases or recurrent adenocarcinoma of the colon and rectum. Dis Colon Rectum 2000;43:759–767.

23. Nguyen M, Varma V, Perez R, et al. CT with histopathologic correlation of FDG uptake in a patient with pulmonary granuloma and pleural plaque caused by remote talc pleurodesis. AJR Am J Roentgenol 2004;182:92–94.