^{18}F-FDG PET for Evaluation of the Treatment Response in Patients with Gastrointestinal Tract Lymphomas

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^{18}F-FDG PET is highly sensitive and specific for evaluation of the treatment response of nodal and extranodal diseases in patients with malignant lymphomas. However, no data are available in the literature with regard to ^{18}F-FDG PET for evaluation of the treatment response in patients with lymphomas with gastrointestinal tract (GIT) involvement. This study was undertaken to investigate the usefulness of ^{18}F-FDG PET in monitoring the response to the treatment of lymphomas in this setting. **Methods:** We retrospectively analyzed 19 patients with different types of lymphomas (10 diffuse large B-cell lymphomas, 4 follicular lymphomas, 3 mantle cell lymphomas, and 2 Hodgkin's disease) involving GIT. Among 19 patients, 4 had gastric involvement, 13 had small bowel involvement, and 2 had small bowel plus colon involvement by lymphomas. All patients underwent ^{18}F-FDG PET before and after the completion of therapy. The results of ^{18}F-FDG PET were compared with the results of CT and clinical outcome; the presence of relapse was determined on the basis of positive biopsy results or clinical follow-up data. **Results:** Of the 19 posttreatment PET scans, 13 showed no pathologic ^{18}F-FDG uptake, whereas 6 showed persistent ^{18}F-FDG uptake. Among the 13 patients who had negative PET scans, only 1 patient (7.7%) relapsed, whereas all 6 patients (100%) who had persistent abnormal ^{18}F-FDG uptake on posttherapy PET scans relapsed. Posttreatment CT scans were negative for 10 patients but showed persistent disease in the remaining 9 patients. Among the 10 patients who had negative CT scans, 9 remained in remission and 1 (10%) relapsed. Of the 9 patients who showed persistent disease, 6 (67%) relapsed and 3 (33%) remained in remission after the mean follow-up of 20 mo. The sensitivity, specificity, positive and negative predictive values, and accuracy of posttherapy ^{18}F-FDG PET were 86%, 100%, 100%, 92%, and 95%, respectively. The corresponding values for CT were 67%, 75%, 75%, 90%, and 79%, respectively. Patients with positive ^{18}F-FDG PET results had statistically significantly lower disease-free survival (DFS) (0%) than did those with positive CT results (33%) ($P = 0.04$). There was no statistically significant difference in DFS between patients with negative ^{18}F-FDG PET results and patients with negative CT results. **Conclusion:** A positive ^{18}F-FDG PET scan after the completion of chemotherapy in patients with lymphomas with GIT involvement is a strong predictor of relapse. ^{18}F-FDG PET has higher diagnostic accuracy than CT in the detection of residual disease after therapy. Despite the mild physiologic ^{18}F-FDG uptake in the GIT, ^{18}F-FDG PET has potential value in monitoring the response to treatment in patients with GIT lymphomas, particularly when pretreatment PET results are positive.

Key Words: gastrointestinal tract; lymphoma; ^{18}F-FDG PET; Hodgkin's disease; non-Hodgkin's lymphoma

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The gastrointestinal tract (GIT) is the most frequently involved extranodal site of non-Hodgkin's lymphoma (NHL). It may be seen initially as primary gastrointestinal lymphoma or as disseminated nodal disease secondarily involving the GIT (*1,2*). Lymphomas can involve any part of the GIT, from the oral cavity to the rectum. The most frequently involved organ is the stomach, followed by the small intestine, colon and, rarely, other gastrointestinal organs, including the pancreas and liver (*3–5*). Thirty percent to 50% of patients with small bowel lymphoma initially present with an abdominal emergency (*6,7*). Approximately one half to two thirds of GIT NHLs are diffuse large B-cell lymphomas (*8*). Hodgkin's disease (HD) does not involve the GIT alone (*9*). The optimal treatment of GIT lymphomas is a most controversial issue and depends on the histologic type and stage of the disease (*10*). Surgical resection can play an important role in the diagnosis and treatment of localized NHL of the GIT (*6*). Radiation is usually reserved for patients with high operative risk and for locally advanced recurrent disease after surgical resection (*4*). Most patients with GIT lymphomas present with residual masses after treatment (*11*).

CT is the most commonly used imaging modality for the management of patients with lymphomas. A decrease in the size of a lymphomatous mass compared with that seen on a pretreatment scan is considered a response to treatment. However, depending on the size of the mass, its location, its histology, and the treatment given, a decrease in size may

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take a long time to appear on CT or may not even occur in the presence of fibrosis, necrosis, and inflammation (*11,12*). Therefore, CT cannot differentiate residual disease from fibrosis. Gallium scintigraphy can differentiate these 2 conditions after treatment in nodal disease but has limited sensitivity in detecting extranodal involvement (*13*). The resolution of gallium scans is also suboptimal; moreover, physiologic uptake of gallium in the GIT can obscure active disease in the abdomen.

Many of the limitations of conventional imaging modalities and gallium scintigraphy for lymphomas can be overcome with ^{18}F-FDG PET. Several studies have shown the effectiveness of ^{18}F-FDG PET for assessment of the treatment response among patients with lymphomas (*14*). Despite the high prevalence of GIT involvement by NHL, only a few studies with a limited number of patients have been published in the literature on the use of ^{18}F-FDG PET in the management of these patients (*15,16*). This study was undertaken to investigate the usefulness of ^{18}F-FDG PET for evaluation of the treatment response in patients with involvement of the GIT primary or secondary to lymphomas.

MATERIALS AND METHODS

Patient Population

From 1999 to 2003, 19 patients who had lymphomas (10 diffuse large B-cell lymphomas, 4 follicular lymphomas, 3 mantle cell lymphomas, and 2 HD) and who had primary or secondary involvement of the GIT were included in this retrospective study. There were 13 men and 6 women (age range, 23–79 y; mean ± SD, 47.5 ± 14 y). Among these 19 patients, 4 had gastric involvement, 13 had small bowel involvement, and 2 had small bowel plus colon involvement by lymphomas. All patients had ^{18}F-FDG PET and CT before and after the completion of therapy. Posttherapy PET and CT scans were obtained within 8 wk after completion of the last chemotherapy treatment. CT and PET scans were performed within 4 wk of each other.

^{18}F-FDG PET Imaging

PET was performed with a dedicated whole-body PET scanner (Allegro; Philips Medical System or ADAC UGM). The patients fasted for at least 4 h, and serum glucose levels were <140 mg/dL in all patients. Patients with serum glucose levels higher than 140 mg/dL were excluded from the study to avoid any false-negative results. Immediately before the PET scan acquisition, all patients were asked to empty their bladders, because patients were imaged without an indwelling urinary catheter. PET was initiated 60 min after intravenous administration of ^{18}F-FDG at 2.516–5.2 MBq (0.068–0.14 mCi)/kg. Sequential overlapping scans were acquired to cover the neck, chest, abdomen, and pelvis. Transmission scans obtained with a ^{137}Cs point source were interleaved between the multiple emission scans to correct for nonuniform attenuation. The images were reconstructed with an iterative reconstruction algorithm, and both attenuation-corrected and non–attenuation-corrected images were interpreted.

^{18}F-FDG PET Image Interpretation

Interpretation of the pre- and posttreatment PET studies included a review of both attenuation-corrected and non-attenuation-corrected scans. Two nuclear medicine physicians who were unaware of other clinical or imaging information independently interpreted the ^{18}F-FDG PET images. Special attention was given to ^{18}F-FDG uptake in the GIT in both pre- and posttreatment studies. Standardized uptake values were calculated for all involved metabolically active sites with a standard formula. The findings were classified as positive or negative depending on the presence or absence of ^{18}F-FDG uptake in the posttreatment PET study compared with the pretreatment PET study. In cases of disagreement between the interpreters' diagnoses, a final decision was made by consensus.

CT Image Interpretation

CT of the head, neck, thorax, abdomen, and pelvis was performed for all patients. Interpretation of the CT images was based on the corresponding written reports, which were compiled from a consensus reading during the daily radiology readout sessions.

Clinical Interpretation of Imaging Results

The standard reference for ^{18}F-FDG PET and CT images was based on biopsy results and clinical follow-up for more than 12 mo beyond the time of the imaging studies. The diagnosis of relapse was based on positive histopathologic examination results in 4 patients and clinical follow-up data in 3 patients. The results of ^{18}F-FDG PET were compared with those of CT.

True-Positive. True-positive included patients with clinical evidence of recurrent or persistent disease, positive ^{18}F-FDG PET and CT studies, positive biopsy results, and clinical follow-up showing persistence or progression of disease.

True-Negative. True-negative included patients who remained in remission for at least 12 mo after the imaging studies and who had negative ^{18}F-FDG PET and CT studies.

False-Positive. False-positive included patients with positive imaging studies despite clinical remission and no recurrence within 12 mo.

False-Negative. False-negative included patients with persistence or recurrence of disease within 12 mo not detected by imaging studies.

Statistical Analysis

We calculated *P* values with the Student *t* test. Sample groups were assigned on the basis of patient PET and CT results. The sample groups were compared on the basis of the numbers of patients who relapsed and those who did not. It was assumed that the variances between the samples were unequal.

Survival curves were generated with the Kaplan–Meier method. Survival was measured as the disease-free proportion in each sample and was plotted as a percentage on the *y*-axis. Duration of follow-up was plotted on the *x*-axis to show overall survival as a function of the follow-up period in months.

RESULTS

Details for all patients, including pre- and posttreatment ^{18}F-FDG PET and CT results as well as follow-up and final outcome, are shown in Table 1. Overall, 16 of 19 patients received chemotherapy alone as the first line of treatment; the remaining 3 had surgery in addition to chemotherapy. Of the 19 patients, 13 had no pathologic ^{18}F-FDG uptake, whereas 6 had persistent ^{18}F-FDG uptake on posttreatment ^{18}F-FDG PET scans obtained within 8 wk of the completion of treatment. Among the 13 patients who had negative

TABLE 1
Summary of ^{18}F-FDG PET and CT Results Before and After Treatment in Patients with Lymphomas with GIT Involvement

Patient	Age (y)	Sex	Diagnosis	Pretreatment results from:		Other lesions	Posttreatment results from:		FU (mo)	Time to relapse (mo)	Outcome
				CT	PET		PET	CT			
1	23	F	HD	Mass within cecum	Ileocecal, ascending colon	Yes	Negative	Negative	38		Remission
2	34	F	HD	Iliocecal, ascending colon	Cecum, ascending colon	Yes	Negative	Negative	24		Remission
3	41	F	FL	Stomach, abdominal	Stomach	Yes	Positive	Positive	14	9	Relapse
4	36	F	FL	Terminal ileum	Distal ileum and cecum	No	Negative	Negative	30		Remission
5	46	M	FL	Small bowel	Small intestine	No	Negative	Negative	21		Remission
6	39	M	DLBCL	Ileum	Small intestine	Yes	Negative	Negative	18		Remission
7	47	F	DLBCL	Small intestine	Small intestine	Yes	Positive	Positive	15	5	Relapse
8	33	M	DLBCL	Thickening of gastric wall	Stomach	Yes	Negative	Negative	18		Remission
9	64	M	DLBCL	Ileocolic, stomach	Mild uptake in ileum and stomach	Yes	Negative	Negative	16	11	Relapse
10	36	M	DLBCL	Thickening of gastric wall	Stomach	Yes	Negative	Positive	12		Remission
11	79	M	DLBCL	Ileocecal	Ileocecal	Yes	Negative	Negative	34		Remission
12	62	M	DLBCL	Small intestine	Mild uptake in intestine	No	Negative	Negative	12		Remission
13	33	M	DLBCL	Rectum	Small intestine	Yes	Negative	Negative	12		Remission
14	59	F	MCL	Small intestine	Small intestine	Yes	Negative	Positive	15		Remission
15	55	M	MCL	Jejunum, terminal ileum	Small intestine	No	Negative	Positive	36		Remission
16	41	M	DLBCL	Distal ileum	Distal ileum	Yes	Positive	Positive	18	11	Relapse
17	57	M	DLBCL	Jejunum, ileum, colon	Ileocecal, ascending colon	Yes	Positive	Positive	6	6	Relapse
18	57	M	FL	Presacral mass	Rectum	Yes	Positive	Positive	9	8	Relapse
19	61	M	MCL	Mural thickening of stomach	Stomach, left hemipelvis	Yes	Positive	Positive	12	10	Relapse

FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; FU = follow-up.

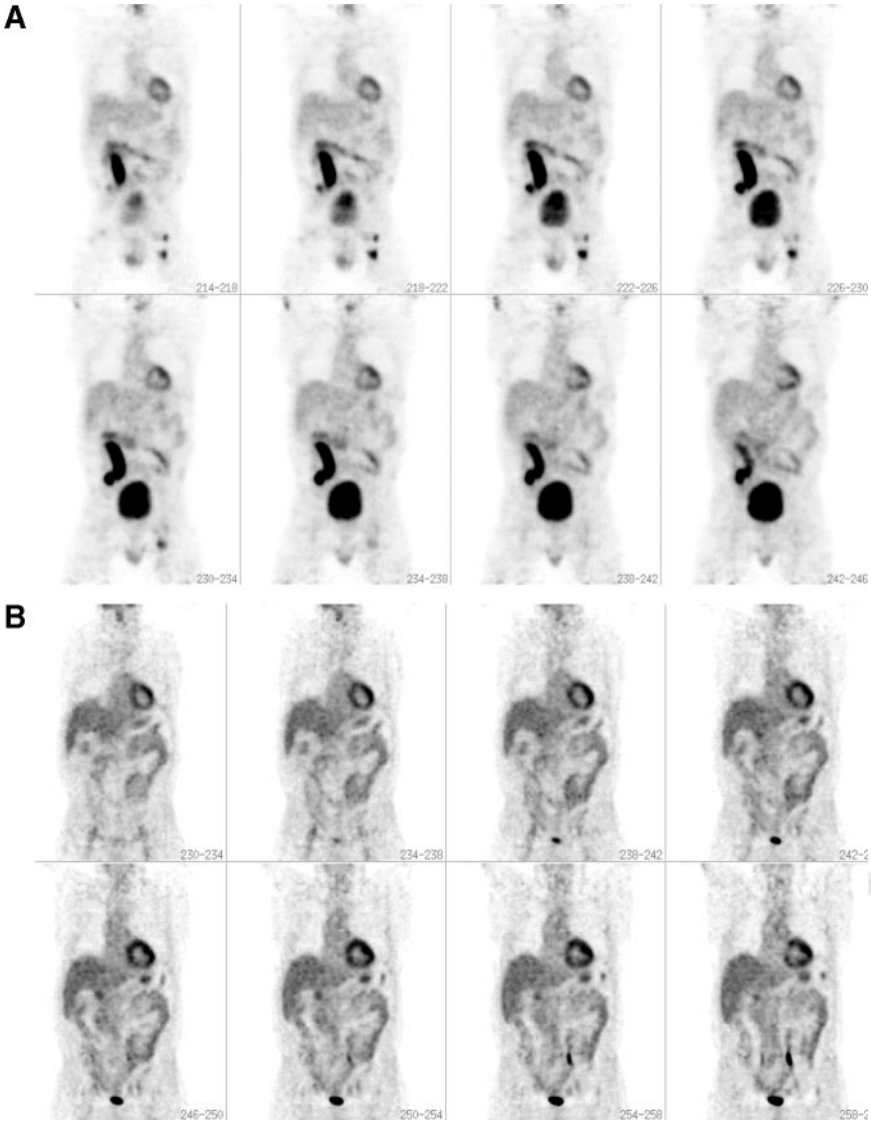

FIGURE 1. (A) Pretreatment ^{18}F-FDG PET scans showing intense ^{18}F-FDG uptake in the region of the cecum and ascending colon. (B) Posttreatment ^{18}F-FDG PET scans showing no abnormal ^{18}F-FDG uptake in the abdomen.

^{18}F-FDG PET findings at the original site of disease, 12 remained in remission after a median follow-up of 22 mo (Fig. 1). One of the 13 patients (7.7%) showed relapse at the original site of disease at 11 mo. All 6 patients who had persistent ^{18}F-FDG uptake at the original site of disease on posttreatment ^{18}F-FDG PET scans (100%) relapsed. The median time to recurrence was 8 mo (range, 6–11 mo). There was a significant difference in disease-free survival (DFS) between patients with positive ^{18}F-FDG PET results and those with negative ^{18}F-FDG PET results (P = 0.000001). The Kaplan–Meier estimate of the disease-free interval in months is shown in Figure 2.

CT was negative for 10 patients, whereas the remaining 9 patients showed persistent disease on posttreatment CT scans obtained within 8 wk after the completion of treatment. Among the 10 patients who had negative CT results at the original site of disease, 9 remained in remission after a median follow-up of 23 mo. One of the 10 patients (10%) showed relapse at the original site of disease at 11 mo.

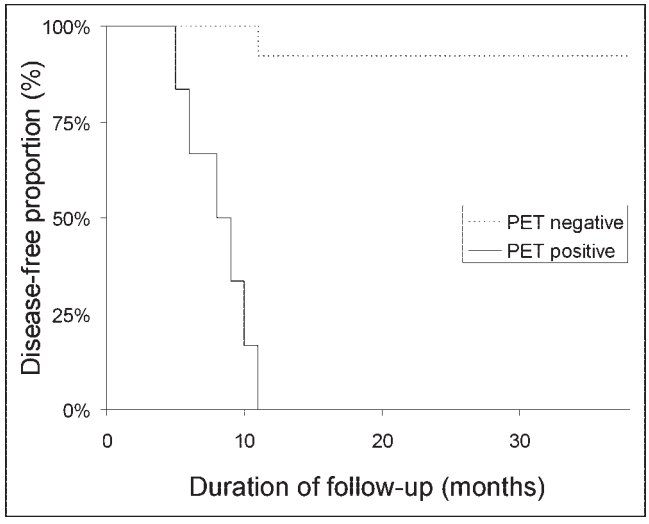

FIGURE 2. Kaplan–Meier estimate of disease-free interval in 13 patients with negative ^{18}F-FDG PET results and 6 patients with positive ^{18}F-FDG PET results. Time intervals are in months.

Among the 9 patients who showed persistent disease at the original site of involvement on posttreatment CT scans, 6 (67%) relapsed in a median time of 8 mo. Three patients who showed persistent disease on CT scans remained in remission after the mean follow-up of 20 mo (range, 12–36 mo) (Fig. 3). There was a statistically significant difference in DFS between patients with positive CT results and those with negative CT results ($P = 0.005$). The Kaplan–Meier estimate of the disease-free interval in months is shown in Figure 4.

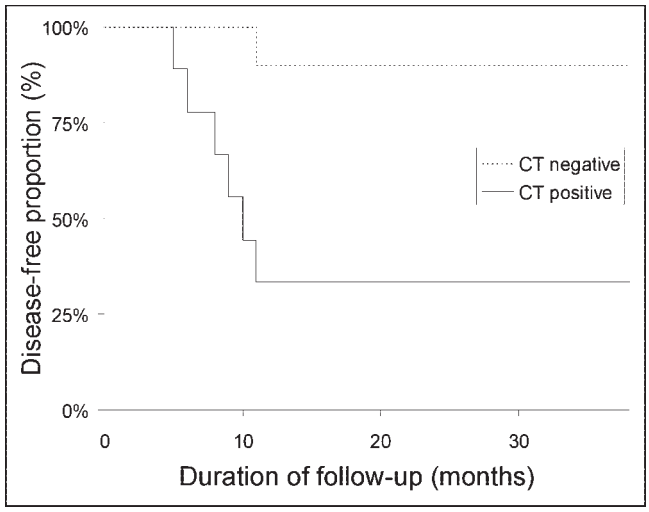

FIGURE 4. Kaplan–Meier estimate of disease-free interval in 10 patients with negative CT results and 9 patients with positive CT results. Time intervals are in months.

Comparison Between ^{18}F-FDG PET and CT

The numbers of true-positive, true-negative, false-positive, and false-negative results of ^{18}F-FDG PET and CT are summarized in Table 2. On the basis of these data, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for posttherapy ^{18}F-FDG PET and anatomic imaging. The sensitivity, specificity, PPV, NPV, and accuracy of ^{18}F-FDG PET were 86%, 100%, 100%, 92%, and 95%, respectively. The corresponding values for CT were 67%, 75%, 75%, 90%, and 79%, respectively. There was a statistically significant difference in DFS between patients with positive ^{18}F-FDG PET results and those with positive CT results (0% vs. 33%) ($P = 0.04$). The Kaplan–Meier estimate of the disease-free interval in months for these patients is shown in Figure 5. There was no statistically significant difference in progression-free survival between patients with negative ^{18}F-FDG PET results and those with negative CT results ($P = 0.8$).

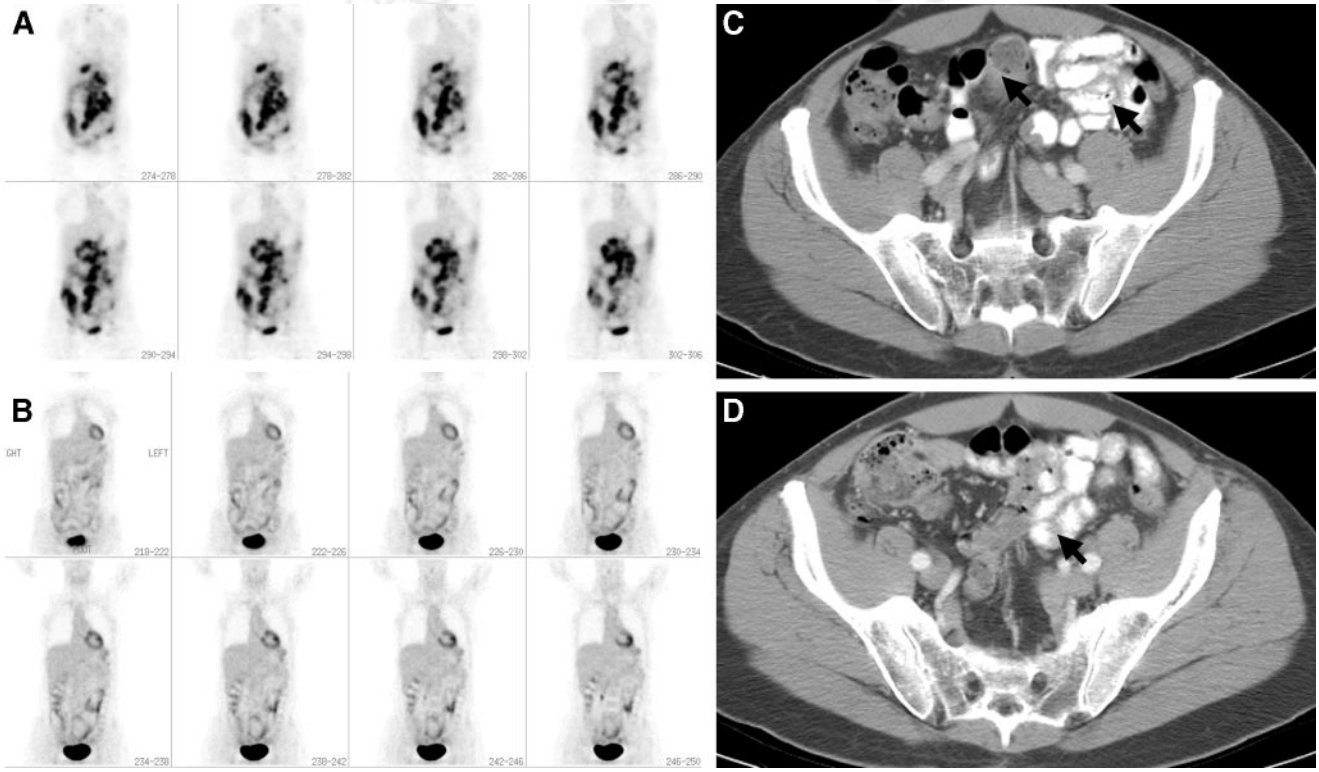

FIGURE 3. (A) Pretreatment ^{18}F-FDG PET scans showing intense irregular ^{18}F-FDG uptake in bowel loops. (B) Posttreatment ^{18}F-FDG PET scans showing no abnormal ^{18}F-FDG uptake in the abdomen. (C) Pretreatment pelvic CT scan of same patient showing irregular wall thickening of small bowel loops (arrow). (C) Posttreatment pelvic CT scan still showing irregular wall thickening of small bowel loops (arrow) suggestive of residual disease, even though ^{18}F-FDG PET scans appeared normal.

TABLE 2
Posttherapy ^{18}F-FDG PET and CT Results

Imaging modality	No. of results that were: True-positive	True-negative	False-positive	False-negative	% Sensitivity	Specificity	PPV	NPV	Accuracy
^{18}F-FDG PET	6	12	0	1	86	100	100	92	95
CT	6	9	3	1	67	75	75	90	79

DISCUSSION

GIT is the most frequently involved extranodal localization in NHL. In the literature published so far, GIT NHL accounts for 4%–20% (on average, 12%–13%) of all NHLs and 30%–40% of all extranodal cases (*1,2*). At autopsy, the GIT is involved in as many as 50% of all patients with generalized NHLs, but most of these patients had subclinical disease (*17*). Evaluation of the treatment response is an important aspect in the management of lymphomas. However, residual masses are frequently observed after treatment, and CT is often unable to discriminate between vital tumor and inactive fibrotic tissue (*11*). Although gallium scintigraphy can play a role in evaluation for the presence of viable tumor in residual posttherapy masses, it also has many limitations, such as suboptimal photon energy, the potential for false-positive findings related to infectious or inflammatory processes, and limited detection of abdominal disease secondary to marked physiologic hepatic and colonic activities (*18,19*). However, PET is able to detect more disease sites above and below the diaphragm than is gallium scintigraphy for the staging of lymphomas (*20*).

^{18}F-FDG PET has been recommended for differentiation between viable residual tumor or recurrent tumor and scar tissue after tumor therapy (*21,22*). ^{18}F-FDG PET may provide superior information for clinical management by enabling biochemical tissue characterization, namely, with high ^{18}F-FDG uptake in viable posttherapeutic lymphoma masses and very low uptake in indolent fibrotic tissue (*22*). The diagnostic accuracy of ^{18}F-FDG PET for assessing the presence of residual disease after therapy is superior to that of CT (*12,18,23*). A positive ^{18}F-FDG PET scan after the end of therapy in HD patients is a strong predictor of relapse. On the other hand, a negative PET scan after the completion of therapy can provide very favorable prognostic information but does not exclude the presence of residual microscopic disease and does not indicate complete remission because of its inability to detect small foci of residual tumor (*23*).

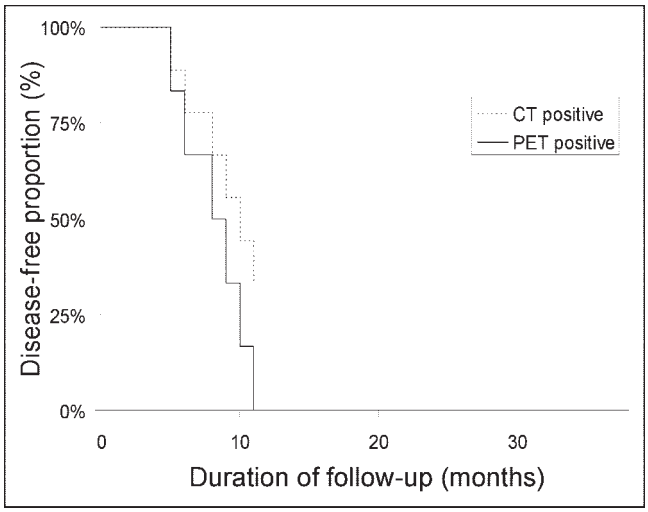

FIGURE 5. Kaplan–Meier estimate of disease-free interval in 6 patients with positive PET results and 9 patients with positive CT results. Time intervals are in months.

The present study demonstrated that ^{18}F-FDG PET had a very high PPV of 100% for evaluation of residual or recurrent disease after treatment. All patients with positive posttherapy ^{18}F-FDG PET scans relapsed within 1 y. However, only 1 patient (7.7%) with negative ^{18}F-FDG PET scans after the completion of therapy relapsed. Accordingly, negative ^{18}F-FDG PET studies and negative CT studies were excellent predictors of a good prognosis. The DFS in patients with negative ^{18}F-FDG PET scans was 22 mo; the DFS in patients with positive scans was 8 mo. Our results are similar to those of previously published reports for patients with nodal lymphomas (*14,23,24*). CT had lower specificity and PPV than did ^{18}F-FDG PET for detecting residual or recurrent disease (75% vs. 100% for both). Among the 9 patients who showed persistent disease at the original site of involvement on the posttreatment CT scans, 3 (33%) remained in remission after the mean follow-up of 20 mo. The DFS rates were much lower in patients with positive ^{18}F-FDG PET scans than in those with positive CT scans ($P = 0.04$).

Morphologic imaging with CT has high sensitivity and specificity for pretreatment staging; however, it has poor specificity for detecting residual or recurrent disease (*23,24*). Cremerius et al. reported that anatomic imaging had a sensitivity of 84% and a specificity of 31% for the detection of residual or recurrent disease after the treatment of malignant lymphomas (*24*). This dramatic decrease in the specificity of CT for posttreatment assessment is attributable to the longer time periods required for nodal and extranodal lesions to normalize in size. Because the detection of disease with ^{18}F-FDG PET is based on metabolism rather than physical size, PET is able to detect posttherapy changes earlier than is conventional anatomic imaging with

CT. We found that 3 patients with negative ^{18}F-FDG PET scans showed persistent disease on CT scans. However, all of these patients had remained in complete remission after the mean follow-up of 20 mo. Therefore, as with nodal lymphomas, a positive CT scan for the assessment of residual disease after the treatment of lymphomatous involvement of GIT has a lower specificity than does a positive ^{18}F-FDG PET scan.

Although ^{18}F-FDG PET is a sensitive imaging technique for detecting NHL in the abdomen, it can be difficult to differentiate nodal disease from intestinal disease on the basis of the pattern of ^{18}F-FDG uptake (*25*). Moreover, the apparent accumulation of ^{18}F-FDG in the GIT may be a spurious finding resulting from a combination of normal peristaltic activity, gastrointestinal lymphoid tissue, and excreted radiotracer within the bowel lumen. Several factors that may produce false-positive results must be taken into consideration; one of these factors is posttreatment inflammatory changes. In the present study, 17 of 19 patients (89%) showed intense ^{18}F-FDG uptake at the site of GIT involvement on pretreatment PET that was much higher than physiologic GIT activity. Only 2 patients (11%) had mildly increased activity, which was similar to physiologic uptake, at the site of disease involvement on CT. One of these 2 patients had false-negative results on posttreatment ^{18}F-FDG PET. None of the patients in the present study had false-positive results.

^{18}F-FDG PET has limited sensitivity in the setting of minimal residual disease (*26*). One of the patients in the present study had false-negative ^{18}F-FDG PET results, although the CT results were also false-negative for that patient. This finding may have been attributable to the presence of microscopic disease at the time of ^{18}F-FDG PET that later led to relapse. In the setting of minimal residual disease, there are fewer tumor cells, which may or may not have increased glucose metabolism, to be detected. In such a setting, ^{18}F-FDG PET and any other imaging modalities would be expected to have higher false-negative rates than biopsy and histologic examination of tissues. ^{18}F-FDG PET requires the presence of a certain number of tumor cells with altered biochemical function to visualize these disease sites (*27*).

Only a few studies with a small number of patients and variable results have been published in the literature on ^{18}F-FDG PET for the evaluation of GIT involvement by lymphoma (*15,16,28–30*). Hoffmann et al. retrospectively analyzed 5 patients with enteropathy-type T-cell lymphomas and demonstrated the potential value of ^{18}F-FDG PET for diagnosing and imaging enteropathy-type T-cell lymphomas (*16*). Sam et al. reported 2 cases of clinically unsuspected small bowel involvement of mantle cell lymphomas that were initially detected on ^{18}F-FDG PET (*28*). Rodriguez et al. performed a study of 8 patients with gastric lymphomas and concluded that ^{18}F-FDG PET can be used as a complement to endoscopy and CT in selected patients; in this setting, PET can yield additional information to determine the choice of therapy (*31*). However, other investigators have reported contradictory results in patients with follicular lymphomas localized in the duodenum and B-cell lymphomas of the mucosa-associated lymphoid tissue type. In these studies, none of the 8 patients with primary duodenal follicular lymphomas and none of the 5 patients with B-cell lymphomas of the mucosa-associated lymphoid tissue type had positive ^{18}F-FDG PET findings (*28,29*). In the present study, ^{18}F-FDG PET scans showed intense ^{18}F-FDG uptake in all 3 patients with follicular lymphomas and in 6 of 8 patients with B-cell lymphomas.

CONCLUSION

A positive ^{18}F-FDG PET scan after the completion of chemotherapy in patients with lymphomas and GIT involvement is a strong predictor of relapse. ^{18}F-FDG PET has a higher diagnostic accuracy than CT for the detection of residual disease after therapy. Despite the mild physiologic ^{18}F-FDG uptake in GIT, ^{18}F-FDG PET has potential value in monitoring the response to treatment in patients with GIT lymphomas, particularly when pretreatment PET results are positive. However, more studies with a larger number of patients are required to confirm the results of our study.

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Errata

In the article "The Role of ^{18}F-FDG PET in Staging and Early Prediction of Response to Therapy of Recurrent Gastrointestinal Stromal Tumors," by Gayed et al. (*J Nucl Med.* 2004;45:17–21), Tables 1 and 2 contain errors. In Table 1, the column headers "CT" and "FDG PET" should have been transposed, and in Table 2, the number of false-negative FDG PET findings should have been reported as 24, not 25. The authors regret the errors.

Because of a proofreading oversight, the book review "IAEA Quality Control Atlas for Scintillation Camera Systems," by William D. Erwin (*J Nucl Med.* 2004;45:1792) failed to name the author of the book, Ellinor Busemann Sokole, PhD, of Academic Medical Center, Amsterdam, The Netherlands. We regret the error.

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