^{18}F-FDG PET Versus CT for the Detection of Enteropathy-Associated T-Cell Lymphoma in Refractory Celiac Disease

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Refractory celiac disease (RCD) can evolve into enteropathy-associated T-cell lymphoma (EATL). ^{18}F-FDG PET has been reported to discriminate between RCD and EATL. Because prospective data are lacking, we designed a prospective study to evaluate the potential of ^{18}F-FDG PET for detection of EATL in patients with RCD and compared the results with those obtained using abdominal CT in a referral center. **Methods:** Between April 2003 and April 2005, 8 consecutive patients (median age, 66 y; range, 52−89 y) with EATL and 30 patients (median age, 61 y; range, 44−71 y) with RCD were included. CT and ^{18}F-FDG PET were performed on all patients. Histologic evidence of EATL was identified in tissue samples obtained during upper gastrointestinal endoscopy or surgical resection. **Results:** Villous atrophy was found in all patients with RCD and all (except 1) patients with EATL in nontumoral mucosa. Histologic examination of 1 patient with EATL localized in the duodenum showed intraepithelial lymphocytosis only. ^{18}F-FDG PET could reveal sites histologically proven to be EATL in all 8 patients, whereas CT showed normal findings in 1 patient with EATL. ^{18}F-FDG PET detected unsuspected extraintestinal sites affected by EATL in 2 patients. CT showed abnormalities such as a thickened small-bowel wall or lymphadenopathy in 14 patients with RCD lacking evidence of EATL at follow-up. ^{18}F-FDG PET findings were positive in 3 and equivocal in another 3 patients with RCD. ^{18}F-FDG PET was more sensitive and specific than CT (100% vs. 87% and 90% vs. 53%, respectively). **Conclusion:** Our data show that ^{18}F-FDG PET is more sensitive in detecting EATL in patients with RCD than is CT. ^{18}F-FDG PET, in addition to conventional CT, is recommended for evaluating patients with RCD.

Key Words: refractory celiac disease; enteropathy-associated T-cell lymphoma; computed tomography; positron emission tomography

J Nucl Med 2006; 47:1622–1627

Refractory celiac disease (RCD), a disease of malabsorption due to persisting villous atrophy despite a gluten-free diet for at least 12 mo (*1,2*), can evolve into enteropathy-associated T-cell lymphoma (EATL) (*3–5*). RCD is reported to occur in 5%−30% of patients with celiac disease (*6*). The relative risk of EATL is 20−30 times higher in patients with celiac disease than in the general population (*7,8*).

Although the value of CT has been retrospectively assessed in patients with celiac disease (*9,10*), its role in detecting EATL has been reported in case reports only (*11*). Moreover, the role of radiologic imaging may be limited in patients with RCD and EATL because the neoplastic changes may be restricted to the epithelial layer of the small bowel even when the lymphoma diffusely affects the whole small intestine (*12*).

^{18}F-FDG PET has become a well-accepted method for diagnosis, staging, and follow-up of patients with malignant lymphomas (*13–16*), with the exception of extranodal marginal-zone B-cell lymphoma of the mucosa-associated lymphoid tissue lymphoma (*17*). ^{18}F-FDG PET seems to discriminate between RCD and EATL (*18*), although data are limited to case reports (*19*) or retrospective analysis of single patients with EATL and RCD (*12*).

Because prospective data are lacking, we designed this longitudinal study to evaluate the potential of ^{18}F-FDG PET for detecting EATL in patients with RCD and compared the results with those obtained by abdominal CT.

MATERIALS AND METHODS

Patients

Between April 2003 and April 2005, 41 consecutive patients were referred to the Department of Gastroenterology for evaluation of RCD and EATL. Three patients were excluded because of normal findings on duodenal histology, ^{18}F-FDG PET, and abdominal CT. Therefore, 38 patients were included in the study; their clinical characteristics are summarized in Table 1.

Received Mar. 15, 2006; revision accepted Jun. 19, 2006.

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TABLE 1
General and Clinical Characteristics of Patients with RCD and EATL

General and clinical characteristics	Total (n = 38)	Patients with RCD (n = 30 [79%])	Patients with EATL (n = 8 [21%])	P
Median age and age range (y)	63 (44−89)	61 (44−71)	66 (52−89)	0.064
Sex, M:F	19:19	14:16	5:3	0.69
Mean body mass index (±SD)	21.8 (±3.1)	21.8 (±3.4)	21.3 (±2.2)	0.61
Number of patients with family history of...				
Celiac disease	1 (2.6%)	1 (3.3%)	—	—
Other malignancy	2 (5.3%)	2 (6.7%)	—	—
Median time and range of time since celiac disease was diagnosed (y)	5 (1−17)	6 (1−17)	3 (1−9)	0.097
Number of patients with autoimmune disease	13 (34.2%)	11 (36.7%)	2 (25%)	0.68
Number of patients with other malignancy	4 (10.5%)	3 (10%)	1 (12.5%)	0.97

The diagnosis of EATL, based on histologic and immunohistochemical features (*18*) according to the recent WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (*20*), was made in 8 patients (21%; 95% confidence interval [CI], 11%–36%). EATL was newly diagnosed in 5 patients and had already been diagnosed at the referring hospital in 3 patients within a median of 4 wk (range, 3−11 wk) preceding evaluation. Histologic evidence of EATL was identified in tissue samples obtained by small-bowel resection (n = 1), small- and large-bowel resection (n = 1), small-bowel and lymph node resection (n = 1), and lymph node resection (n = 2). In 3 patients, EATL lesions were recognized in small-bowel biopsy samples obtained during upper gastrointestinal endoscopy.

Thirty patients (79%; 95% CI, 63%–88%) were considered to have RCD because symptoms of malabsorption were due to persisting villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes despite adherence to a gluten-free diet (*2*) and in the absence of histologic evidence of EATL. Surgery was performed on 2 patients with RCD (1 patient with mesenteric infiltration and 1 with abdominal lymphadenopathy), without identifiable evidence of EATL in the resectioned material.

Methods

The diagnostic work-up included the celiac disease–specific serum antibody tests (IgA-antigliadin (*21,22*), -transglutaminase (*23,24*), and -endomysium antibodies (*23*)), human leukocyte antigen, DQ subregion 2 or 8 typing (*23,25*), and small-bowel histologic evaluation according to the modified Marsh classification (*26,27*). Suspected sites of lymphoma were sampled during small-bowel enteroscopy or surgery for histologic examination when indicated.

All candidates underwent abdominal CT and ^{18}F-FDG PET as part of the diagnostic work-up. The CT examinations were performed with a Somatom volume zoom Sensations 64 (Siemens). The patients fasted overnight. A diluted solution of oral barium sulphate suspension (1,000 mL of E.Z.-CAT) was administered to the patients; it was divided into 2 doses (500 mL) administered the night before the scan and the morning of the investigation. The patients were administered additional E.Z.-CAT (200 mL) 15 min before the CT started and 100 mL of intravenous iopromide (300 mg/mL). Two experienced radiologists analyzed abdominal CT, after reaching a consensus, for bowel wall thickening (abnormal, >3 mm thick; Fig. 1), lymphadenopathy (abnormal, >10 mm in size along the short axis; Fig. 2), and mesenteric fat infiltration (Fig. 3). CT findings were considered abnormal when one or a combination of these abnormalities was found.

Whole-body ^{18}F-FDG PET was performed using a dedicated PET scanner (ECAT EXACT HR+; CTI/Siemens). All patients were asked to fast for at least 6 h before ^{18}F-FDG injections and received an intravenous injection of 20 mg of *N*-butylbromide (Buscopan; Boehringer Ingelheim) for smooth-muscle relaxation 5 min before the start of the scan (*28*). This injection was repeated when necessary 45 min after the first injection. Emission and transmission scans of 5 and 4 min per bed position (ETTE mode) were performed 60 min after injection of 370 MBq of ^{18}F-FDG (555 MBq when body weight was >85 kg) from the neck to the pelvic floor. All emission scans were corrected for decay, scatter, randoms, and attenuation and were reconstructed using ordered-subset expectation maximization with 2 iterations and 16 subsets followed by smoothing of the reconstructed image using a gaussian filter of 5 mm in full width at half maximum. Transmission data were smoothed by a 1-dimensional filter in the axial direction and were segmented, and attenuation correction factors were calculated by forward projection. Images were reconstructed iteratively.

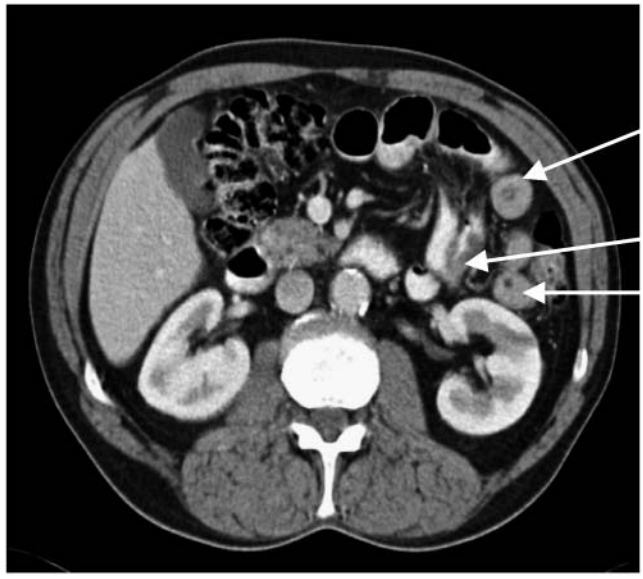

FIGURE 1. Axial abdominal CT image showing thickened small-bowel segments (arrows) in patient with EATL.

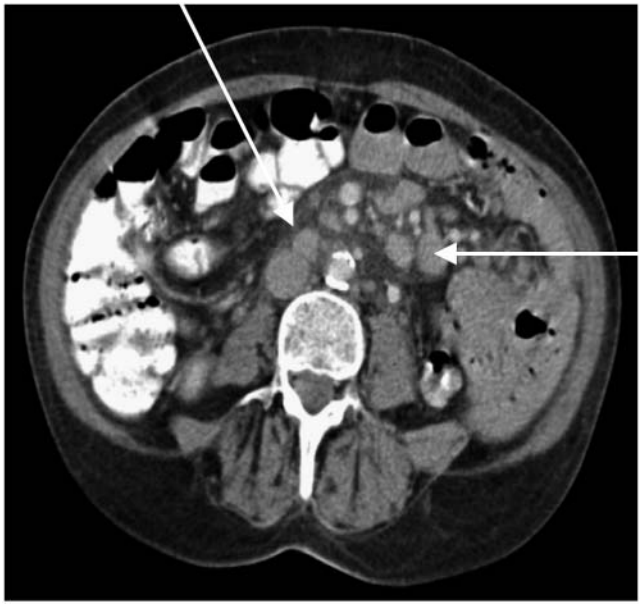

FIGURE 2. Axial abdominal CT image showing enlarged lymph nodes (arrows) in patient with EATL.

Venous blood was withdrawn before injection for measurement of the serum glucose concentration. Two independent nuclear medicine physicians who were unaware of the clinical data and histologic findings interpreted the images. The results of ^{18}F-FDG PET were classified as negative (when ^{18}F-FDG uptake was compatible with physiologic biodistribution), equivocal, or positive (when ^{18}F-FDG uptake was not compatible with physiologic biodistribution and was moderately or intensely increased; Fig. 4). No standardized uptake values were calculated because no validated methods exist for correction of the partial-volume effect of the radioactivity concentration of small volumes such as the small-intestinal wall (smaller than 2 times the resolution of the system). ^{18}F-FDG PET results were compared with those of abdominal CT, histologic findings on biopsy or resection material, and surgical findings.

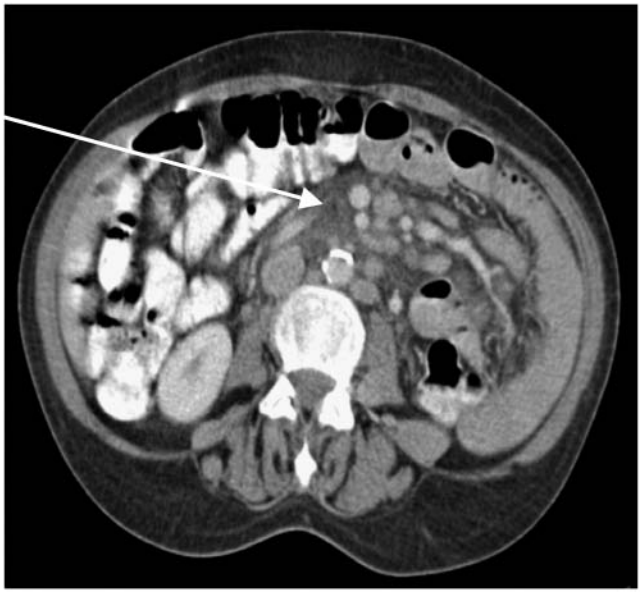

FIGURE 3. Axial abdominal CT image showing mesenteric fat infiltration (arrow) in patient with EATL.

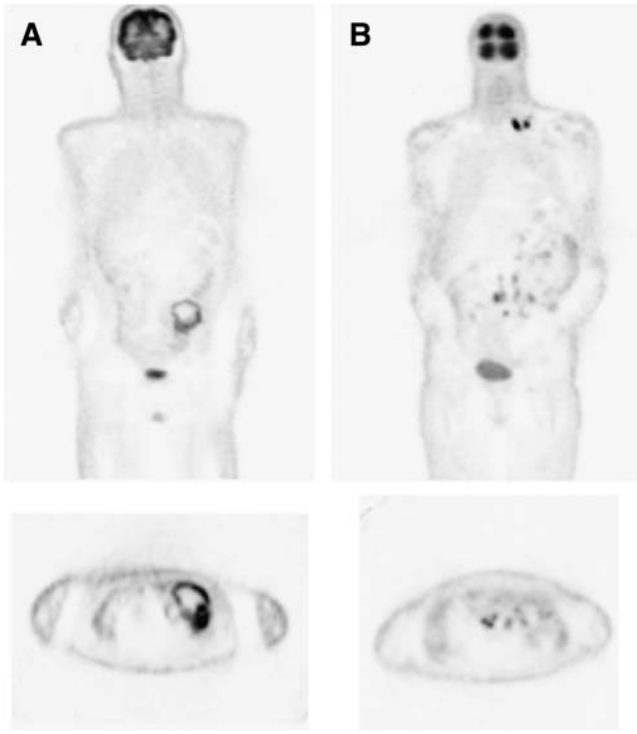

FIGURE 4. Intensely increased ^{18}F-FDG PET uptake on coronal and axial images in patient with small-bowel lymphoma (A) and another patient with abdominal and extraabdominal lymphoma (B).

Informed consent was obtained from all patients, and the institutional review board of the VU University Medical Center gave permission for this study.

Statistical Analysis

The Student paired *t* test, Mann–Whitney test, or Fisher exact test was used for data analysis when indicated. *P* values of less than 0.05 were considered statistically significant. All statistical analysis was performed using the Statistical Software Package, version 11.0 (SPSS Inc.).

RESULTS

Patients

Small-bowel biopsy established the presence of villous atrophy (Marsh III) in all patients with RCD and all (except 1) patients with EATL in nontumoral mucosa. In 1 patient with EATL localized in the duodenum, histologic examination showed only Marsh I changes in the mucosa. The diagnostic makeup of the study population is summarized in Table 2. Within a median follow-up period of 14 mo (range, 9−24 mo), 6 patients (75%) with EATL and 4 patients (13%) with RCD have died ($P = 0.001$). Causes of death in RCD patients were recurrent infections in malnourished patients ($n = 3$) and a metastasized squamous cell lung carcinoma ($n = 1$). Four patients with EATL received therapy consisting of cyclophosphamide, doxorubicin,

TABLE 2
The Celiac Disease Makeup of Patients with RCD and EATL

Diagnostic makeup of celiac disease	Total (n = 38)	Patients with RCD (n = 30 [79%])	Patients with EATL (n = 8 [21%])	P
Number of patients positive to...				
Any serologic test	16 (42.1%)	12 (40.0%)	4 (50.0%)	0.69
IgA antigliadin antibodies	10 (26.3%)	7 (23.3%)	3 (37.5%)	0.41
IgA tissue transglutaminase antibodies	10 (26.3%)	10 (33.3%)	0	0.08
IgA endomysial antibodies	9 (23.7%)	8 (26.7%)	1 (12.5%)	0.65
Number of patients positive to...				
HLA-DQ2 heterozygote	20 (52.6%)	17 (56.7%)	3 (37.5%)	0.43
HLA-DQ2 homozygote	13 (34.2%)	10 (33.3%)	3 (37.5%)	1.0
HLA-DQ8 heterozygote	2 (5.3%)	1 (3.3%)	1 (12.5%)	0.38
HLA-DQ2/DQ8 heterozygote	3 (7.9%)	2 (6.7%)	1 (12.5%)	0.51
Number of patients with small-bowel histology compatible with...				
Marsh I	1 (2.6%)	0	1 (12.5%)	0.21
Marsh IIIa	14 (36.8%)	13 (43.3%)	1 (12.5%)	0.21
Marsh IIIb	12 (31.6%)	9 (30%)	3 (37.5%)	0.68
Marsh IIIc	11 (28.9%)	8 (26.7%)	3 (37.5%)	0.66

HLA-DQ = human leukocyte antigen, DQ subregion.

vincristine, and prednisolone (*20,29*). In 1 patient with EATL, autologous peripheral stem cell transplantation was performed, and no further therapy was given to 3 patients because of their poor general condition and comorbidity.

^{18}F-FDG PET Versus Abdominal CT

In all 8 patients with EATL, ^{18}F-FDG PET identified enhanced abdominal ^{18}F-FDG uptake (100%; 95% CI, 67%–100%), whereas abdominal CT findings were abnormal in 7 of these 8 patients (87%; 95% CI, 52%–97%). Abnormal CT findings in patients with evidence of EATL included lymphadenopathy (n = 4), a thickened small-bowel wall (n = 7), and mesenteric fat infiltration (n = 2). Small-bowel thickening, whether duodenal (n = 2), jejunal (n = 1), jejunal and ileal (n = 3), or diffuse (n = 1), ranged from 8 to 15 mm on CT slices. The abdominal sites of enhanced ^{18}F-FDG uptake were proven to be EATL by histologic examination of samples obtained by surgery or endoscopy. CT did not show any abnormality in 1 patient with EATL proven by surgical resection of the small bowel. In 2 patients with EATL, additional sites of focal ^{18}F-FDG accumulation were shown in the superior mediastinum on ^{18}F-FDG PET images. Mediastinal lymphadenopathy was verified by thoracic CT. Mediastinoscopy and lymph node resection proved the presence of EATL in these 2 patients.

In patients with RCD, ^{18}F-FDG PET findings were positive in 3 (10%; 95% CI, 3%–25%) and CT findings were abnormal in 14 (46.6%; 95% CI, 30%–63%). Of the patients with RCD and positive ^{18}F-FDG PET results, the findings on abdominal CT were normal in 1 and abnormal in 2 patients (1 patient with a 6-mm thickened jejunal wall and 1 patient with a 7-mm thickened jejunal and ileal wall). All patients underwent small-bowel enteroscopy. No histologic evidence of EATL was found. The first 2 patients are alive and in good condition. The third patient died after recurrent chest infections.

In addition, ^{18}F-FDG PET showed equivocal findings in 3 patients (10%; 95% CI, 3%–25%) with RCD. In these patients, the findings on abdominal CT were normal in 1 and abnormal in 2 patients (1 patient with lymphadenopathy and 1 patient with lymphadenopathy and a 10-mm thickened jejunal and ileal wall). The first patient could not undergo further invasive diagnostic examinations because of a poor general condition requiring long-term clinical admission. The other 2 patients underwent small-bowel enteroscopy. No evidence of EATL was found in any of multiple small-bowel histology specimens. Both patients are alive and in good general condition.

Of the patients with normal ^{18}F-FDG PET findings, 10 had abnormal abdominal CT findings. CT showed lymphadenopathy in 3, a thickened small bowel (7−11 mm) in 7, and infiltrated mesenteric fat in 1 patient. Surgical resection of enlarged lymph nodes in 1 patient and mesenteric fat in 1 patient did not show evidence of EATL.

The CT and ^{18}F-FDG PET findings in patients with RCD and those with EATL are summarized in Table 3. Abdominal CT results were concordant with the results of ^{18}F-FDG PET in 7 patients (87.5%) who had EATL and in 18 patients (60%) with RCD. CT results did not match the results of ^{18}F-FDG PET in 1 patient (12.5%) with EATL and 12 patients (40%) with RCD. Table 4 summarizes the sensitivity, specificity, and positive and negative likelihood ratios for CT and ^{18}F-FDG PET. When equivocal ^{18}F-FDG PET findings were scored as positive in the analysis (n = 6 [20%]; 95% CI, 9–37), the specificity declined to 80% but remained higher than that of CT (P = 0.008).

TABLE 3
Abdominal CT and ^{18}F-FDG PET Scan Findings in Patients With and Without EATL

Finding	Number of findings			*P*
	Total (*n* = 38)	Patients with RCD (*n* = 30 [74%])	Patients with EATL (*n* = 8 [26%])	
CT				
Abnormal scan	21 (55.3%)	14 (46.7%)	7 (87.5%)	0.04
Thickened wall	18 (47.4%)	11 (36.7%)	7 (87.5%)	0.01
Lymphadenopathy	8 (21.1%)	4 (13.3%)	4 (50.0%)	0.04
Mesenteric infiltration	3 (7.9%)	1 (3.3%)	2 (25.0%)	0.10
Other	8 (21.1%)	5 (16.7%)	3 (37.5%)	0.32
^{18}F-FDG PET				
Abnormal positive	11 (28.9%)	3 (10.0%)	8 (100%)	<0.001
Equivocal positive	3 (7.9%)	3 (10.0%)	—	—

DISCUSSION

The results of this prospective cohort demonstrated that ^{18}F-FDG PET revealed sites affected by EATL as confirmed on biopsy in all patients, whereas CT was false negative in 1 patient. Conversely, CT showed abnormalities such as a thickened small-bowel wall or lymphadenopathy in 14 patients with RCD lacking evidence of EATL after a follow-up period of at least 1 y, rendering CT less specific than PET, even when equivocal ^{18}F-FDG PET findings were considered positive. Finally, ^{18}F-FDG PET could unravel extraintestinal sites affected by EATL.

Our results confirm earlier conclusions that ^{18}F-FDG PET can detect EATL in patients with RCD (*12*), in contrast to the limited diagnostic role of ^{18}F-FDG PET in mucosa-associated lymphoid tissue lymphoma (*17*). This confirmation indicates that ^{18}F-FDG PET efficacy varies with the histologic type (*30*). However, false-positive ^{18}F-FDG PET readings were made in patients with RCD in the absence of histologic evidence of EATL. It has been reported that false-positive results may be due to inflammation (*31*) or increased uptake in nonrelaxed muscles such as the gut (*30*). In this study, even though we tried, by the routine use of Buscopan, to diminish the effect of small-bowel peristalsis on images obtained during ^{18}F-FDG PET, instances of false-positive findings occurred. Therefore, ^{18}F-FDG PET cannot be a substitute for histologic examination in the diagnosis of EATL. However, ^{18}F-FDG PET can be helpful tool in directing biopsy.

CT abnormalities that have been reported in patients with celiac disease include jejunoileal fold-pattern reversal (*9*), small-bowel intussusception (*32*), lymphadenopathy (*33*), and bowel wall thickening (*10*). Mesenteric nonneoplastic, histologically proven lymphadenopathy or fat infiltration was seen in 2 patients with RCD, suggesting that such findings can accompany RCD without necessarily being specific for T-cell lymphoma (*18*). Moreover, disappearance of benign mesenteric lymph node enlargement and cavitation after a gluten-free diet has been described (*34,35*).

Recently, hybrid PET/CT devices have been introduced as a powerful tool to facilitate fusion of the functional information of PET with the anatomic information of CT (*36*). Further, PET/CT as a combined modality may contribute substantially to lesion characterization and staging in patients with lymphoma (*37*). Whether combined PET/CT improves the diagnostic distinctions described for patients with EATL needs to be further investigated.

To our knowledge, this study was the largest series of patients with RCD and EATL being investigated by ^{18}F-FDG PET for detection or exclusion of EATL. The relatively limited number of patients may be considered a confounding factor to the main outcome of the study. However, the prospective nature of the study and the available

TABLE 4
Diagnostic Value of CT vs. ^{18}F-FDG PET in Detecting EATL in Patients with RCD

Parameter	Abnormal or positive in EATL group (*n*)	Sensitivity (%)	Abnormal or positive in RCD group (*n*)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Abdominal CT	7/8	87.5 (52−97)	14/30	53.3 (36−69)	1.87 (1.17−2.98)	0.23 (0.03−1.51)
Positive ^{18}F-FDG PET	8/8	100 (67−100)	3/30	90 (74−96)*	10 (3.41−29.25)	0.0
Positive and equivocal ^{18}F-FDG PET	8/8	100 (67−100)	6/30	80 (62−90)†	5 (2.4−10.2)	0.0

*P = 0.001 for specificity of positive ^{18}F-FDG PET compared with CT.
†P = 0.008 for specificity of positive and equivocal ^{18}F-FDG PET compared with CT.
Data in parentheses are 95% CI.

follow-up data validate, in our opinion, the reported results. The selection bias inherent in this study because of the strict inclusion criteria might lead to an overestimation of the performance of ^{18}F-FDG PET. Therefore, the generalizability of the study results remains to be elucidated.

CONCLUSION

^{18}F-FDG PET seems a more sensitive method than CT for detecting EATL in patients with RCD. This technique is recommended in addition to conventional CT for evaluating patients with RCD. Positive PET results in patients with RCD should be pursued vigorously by examining histologic samples from areas with high uptake.

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