Brief report

Utility of FDG-PET scanning in lymphoma by WHO classification

Rebecca Elstrom, Liang Guan, Gary Baker, Khozaim Nakhoda, Jo-Anne Vergilio, Hongming Zhuang, Stephanie Pitsilos, Adam Bagg, Lisa Downs, Amit Mehrotra, Scott Kim, Abass Alavi, and Stephen J. Schuster

We retrospectively evaluated ^{18}fluoro-2-deoxyglucose positron emission tomography (FDG-PET) scans in 172 patients with lymphoma and correlated results with pathologic diagnosis using the World Health Organization (WHO) classification system. In total, FDG-PET detected disease in at least one site in 161 patients (94%) and failed to detect disease in 11 patients (6%). The most frequent lymphoma diagnoses were diffuse large B-cell lymphoma (LBCL; n = 51), Hodgkin lymphoma (HL; n = 47), follicular lymphoma (FL; n = 42), marginal zone lymphoma (MZL; n = 12), mantle cell lymphoma (MCL; n = 7), and peripheral T-cell lymphoma (PTCL; n = 5). FDG-PET detected disease in 100% of patients with LBCL and MCL and in 98% of patients with HL and FL. In contrast, FDG-PET detected disease in only 67% of MZL and 40% of PTCL. Comparison with bone marrow biopsies showed that FDG-PET was not reliable for detection of bone marrow involvement in any lymphoma subtype. (Blood. 2003;101:3875-3876)

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Introduction

Computed tomography (CT) scanning and histopathologic examination of bone marrow comprise the current approach to initial staging and evaluation of response to therapy of lymphomas. However, the utility of these modalities is limited, because criteria for disease involvement by CT scan are usually based on the size of a lesion, and bone marrow examination may be limited by sampling error. Furthermore, it may be difficult to distinguish residual disease from nonmalignant "scar" tissue following treatment or to differentiate inflammatory from malignant lesions by CT.

Cancer imaging by positron emission tomography (PET) using ^{18}fluoro-2-deoxyglucose (FDG) is based on the observation that most cancers, including many lymphomas, metabolize glucose at an abnormally high rate.[1] FDG-PET is becoming widely used in the evaluation of patients with lymphoma.[2-4] Although most lymphomas can be imaged by FDG-PET, we and others have observed cases that lack FDG uptake. Previous studies evaluating the sensitivity of FDG-PET in lymphomas showed conflicting results, particularly in indolent lymphomas.[5-11]

We hypothesized that biologic differences between specific pathologic subtypes of lymphoma result in different degrees of FDG uptake and that utility of FDG-PET imaging varies between specific lymphomas. We retrospectively studied results of FDG-PET scans in patients with lymphoma using the World Health Organization (WHO) classification system to identify the specific subtypes reliably detected by FDG-PET. Furthermore, the ability of FDG-PET to detect bone marrow involvement by various lymphoma subtypes was evaluated by comparison with bone marrow biopsy.

Study design

Patients

All FDG-PET scans performed on patients with a diagnosis of non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) at the University of Pennsylvania were selected for study. For cases with a confirmed diagnosis of lymphoma using the WHO classification system, FDG-PET scans performed at initial diagnosis or at relapse prior to treatment were included. Pathology specimens were reviewed, and diagnosis was confirmed by a hematopathologist at the Hospital of the University of Pennsylvania. Cases were excluded if patients had received therapy for lymphoma within 6 months of FDG-PET scanning or if all identifiable lesions had been removed surgically. The study was approved by the University of Pennsylvania Institutional Review Board.

FDG-PET scanning

PET imaging was performed using a C-PET scanner (ADACUGM, Philadelphia, PA). Patients fasted for at least 4 hours, and serum glucose levels were within normal range in all cases. The scan was begun 60 minutes after intravenous administration of 2.516 MBq (0.068 mCi/kg) FDG. Sequential overlapping scans were obtained covering the neck, chest, abdomen, and pelvis. Transmission scans using a Cesium 137 point source were interleaved between the multiple emissions to correct for nonuniform attenuation correction. The images were reconstructed using ordered subset expectation maximization algorithm. Scans were considered positive if the specific uptake value (SUV) of a suspicious lesion was more than 2.5. The absolute number and percentage of positive scans overall and by WHO classification were determined.

Bone marrow comparison

Comparison of FDG-PET and iliac crest bone marrow biopsy was performed on all patients with large B-cell lymphoma (LBCL), follicular lymphoma (FL), Hodgkin lymphoma (HL), marginal zone lymphoma (MZL), and mantle cell lymphoma

From the Abramson Family Cancer Research Institute of the University of Pennsylvania, Philadelphia; and the Departments of Medicine, Nuclear Medicine, and Laboratory Medicine and Pathology, University of Pennsylvania Medical Center, Philadelphia.

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Reprints: Rebecca L. Elstrom, Division of Hematology/Oncology, University of Pennsylvania, 16 Penn Tower, 3400 Spruce St, Philadelphia, PA 19104; e-mail: relstrom@mail.med.upenn.edu.

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Table 1. PET scan results by WHO classification

Histology	Positive	Negative	Total	% Positive
LBCL	51	0	51	100
FL	41	1	42	98
HL	46	1	47	98
MZL	8	4	12	67
MCL	7	0	7	100
ALCL	2	0	2	100
PTCL	2	3	5	40
CBCL	0	2	2	0
MF	1	0	1	100
BL	1	0	1	100
SLL	1	0	1	100
T/NK	1	0	1	100
Total	161	11	172	94

ALCL indicates anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma; CBCL, cutaneous B-cell lymphoma; MF, mycosis fungoides; BL, Burkitt lymphoma; SLL, small lymphocytic lymphoma; and T/NK, T/natural killer cell lymphoma.

(MCL) for whom biopsy material was available for review. PET scans were reviewed as described in "FDG-PET scanning," and bone marrow was considered positive by FDG-PET if any area of bone marrow showed an SUV more than 2.5. Bone marrow biopsies were reviewed along with diagnostic specimens.

Results and discussion

A total of 172 patients met criteria for analysis (Table 1). FDG-PET imaging detected disease in at least one site in 100% of patients with LBCL (n = 51) and MCL (n = 7) and in 98% of patients with HL (n = 47) and FL (n = 42). The single HL case not detected by FDG-PET was in early relapse documented by biopsy of a subcentimeter subpleural pulmonary nodule. The single case of undetected FL consisted of an ileal tumor detected only by endoscopic biopsy. These cases suggest that tumor volume may be a factor in false-negative FDG-PET studies. FDG-PET also detected disease in patients with ALCL (n = 2), MF (n = 1), BL (n = 1), SLL (n = 1), and T/NK (n = 1); however, the numbers of patients with these diagnoses are too small to assess the utility of FDG-PET. In contrast, only 67% of MZL (n = 12) and 40% of PTCL (n = 5) were detected by FDG-PET. Two cases of low-grade CBCL were also not detected by FDG-PET.

FDG-PET imaging was further evaluated for accuracy in detection of bone marrow involvement by comparing results with iliac crest bone marrow biopsy in the most common histologic subtypes: LBCL, FL, HL, MZL, and MCL. Detection of bone marrow involvement by FDG-PET was suboptimal for all pathologic subtypes of lymphoma examined. Bone marrow biopsies were available for 105 of 159 patients with these histologies. As shown in Table 2, PET rarely detected pathologically identifiable marrow involvement by FL and did not detect marrow involvement by MCL or MZL in any case. This situation may be due to relatively low FDG uptake per cell or to diffuse, low-density marrow involvement by tumor. HL and LBCL, conversely, showed FDG uptake in bone marrow that was not confirmed by iliac crest biopsy in several cases. Although these cases may represent false-positives, patients may alternatively have had patchy bone marrow involvement that was not detected by blind iliac crest biopsy. Whether FDG-PET may in fact improve sensitivity of disease detection in these histologies over blind iliac crest biopsy is an important question that is currently under investigation.

Table 2. Comparison of PET to iliac crest bone marrow biopsy in detection of lymphoma in bone marrow

	Concordant		Discordant		
Histology	Positive	Negative	PET positive, biopsy negative	PET negative, biopsy positive	Total
LBCL	6	21	1	4	32
FL	1	21	0	7	29
HL	0	28	4	0	32
MCL	0	4	0	3	7
MZL	0	3	0	2	5

Other groups have reported conflicting results regarding the utility of FDG-PET imaging in indolent lymphomas.[12,13] However, lymphoma diagnosis by the WHO classification was not reported in these studies. Our data indicate that WHO classification of lymphomas is crucial in determining the utility of FDG-PET to image lymphomas. We suggest that biologic characteristics intrinsic to specific histologic subtypes determine glucose utilization and, therefore, FDG uptake. The fact that FL almost invariably showed high FDG uptake demonstrates that histologic grade is not the most important predictor of FDG avidity. Similarly, the variability of results within MZL and PTCL suggests that the mechanisms of metabolic deregulation during lymphomagenesis are more complex than simply meeting the cellular needs of growth and proliferation.

The identification of lymphomas that are uniformly detected by FDG-PET implies that this imaging modality may be useful in detecting residual active disease for specific lymphomas even in the absence of a baseline scan. Confirmation of our results in prospective studies of larger numbers of patients and in multiple centers is needed before conclusions derived from these results can be adopted into clinical practice.

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