

Positron Emission Tomography with 18-Fluorodeoxyglucose in the Staging and Follow-up of Lymphoma in the Chest

Markus Bangerter, Jörg Kotzerke, Martin Griesshammer, Klaus Elsner, Sven Norbert Reske and Lothar Bergmann

From the Departments of Medicine III—Hematology, Oncology, Clinical Immunology and Infectious Disease (M. Bangerter, M. Griesshammer, L. Bergmann), Nuclear Medicine (J. Kotzerke, S. N. Reske), and Radiology (Klaus Elsner), University of Ulm, Germany

Correspondence to: Markus Bangerter, MD, Department of Medicine III, University of Ulm, Robert-Koch-Str. 8, D-89081 Ulm, Germany. Tel: + 49 731 50 24 410. Fax: + 49 731 50 24 405. E-mail: markus.bangerter@medizin.uni.ulm.de

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The purpose of this retrospective study was to evaluate the accuracy of positron emission tomography (PET) using 18-F-fluorodeoxyglucose (FDG) in predicting lymphomatous involvement in the hilar and mediastinal regions in the staging and follow-up of patients with malignant lymphoma. One hundred forty-seven thoracic PET studies in 89 consecutive lymphoma patients were reviewed. Static FDG-PET imaging was performed following application of 270 MBq FDG (mean). Results of FDG-PET were compared with the findings of computed tomography (CT) in all patients and clinical follow-up examination. Eighty-nine of 147 (60%) PET studies showed no FDG uptake in the hilar or mediastinal regions, while 58 (40%) studies did detect FDG uptake in these regions. In 52 of 58 abnormal studies (90%), lymphomatous involvement of the hilar and/or mediastinal regions seen by CT was present. In the remaining six abnormal PET studies (10%), FDG uptake was considered as false-positive because of missing lesions on corresponding CT scans. In four patients false-positive FDG uptake was observed before treatment, in two patients after completion of therapy. In these two patients FDG uptake after therapy was caused by thymus hyperplasia. The remaining four cases before treatment remained unresolved. Sensitivity of FDG-PET was 96%, specificity 94%, positive predictive value 90%, and negative predictive value 98%, respectively. The present study suggests that FDG-PET has potential value in predicting lymphomatous involvement in the hilar and mediastinal regions. FDG-PET may obviate invasive diagnostic procedures in patients with lymphoma.

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In recent years the prognosis for patients with malignant lymphoma has markedly improved, not only as a result of our increased understanding of histopathologic patterns and new therapeutic concepts, but because of our recognition of parameters for accurately defining the spread of disease. Gallium citrat (Ga-67) scintigraphy has an important role in monitoring patients' response to treatment and in detecting residual active lymphoma, especially in the mediastinum (1–8). The current role of Ga-67 scintigraphy as part of staging work-up remains controversial, because sensitivity is decreased especially in the abdomen owing to hepatic uptake and excretion into the bowel (9–11). The specificity of Ga-67 scintigraphy is also limited because of uptake by normal tissue, especially in the pulmonary hila (5, 12–15). The reason for false-positive uptake, in these studies called benign Ga-67 uptake, is presently unknown but it poses a diagnostic dilemma, especially in the monitoring of treatment results. In 15 out of 23 lymphoma

patients evaluated by Chapman et al. (13) the hilar uptake was not associated with active lymphoma. Even-Sapir et al. (15) correlated the uptake of Ga-67 in the hilar of lymphoma patients with computed tomography (CT) and follow-up examinations. In 59 of 107 thoracic single photon emission computed tomography (SPECT) studies Ga-67 uptake was detected in the hilar and mediastinal regions. In 39 of these 59 studies Ga-67 uptake was benign without active disease (66%).

Positron emission tomography (PET) with 2-[F-18]-fluoro-2-deoxy-D-glucose (FDG) has been increasingly used to measure regional glucose metabolism in malignant tumors (16–30). FDG is an analog of D-glucose that competes with glucose for facilitated intracellular transport and phosphorylation by hexokinase (31). Hence, FDG accumulates intracellularly, allowing malignant tumors such as lymphoma to be imaged. In recent years FDG-PET has been successfully used for imaging of lymphoma

(20–30). Recently, we showed that FDG-PET is a sensitive method in the staging in lymphoma patients (20). In 60 patients with untreated lymphoma, PET detected, in concordance with CT, 30 lymphomatous lesions in the hilar and mediastinal regions. However, the specificity of this new non-invasive imaging method could be limited because of uptake of FDG in benign lesions, necrosis, thymus hyperplasia or inflammatory conditions (31–37).

We initiated the present study in order to investigate the role of FDG-PET in predicting lymphomatous involvement in the hilar and mediastinal regions in patients with malignant lymphoma before and after treatment.

MATERIAL AND METHODS

Patients

In 89 patients (40 females, 49 males; age range 14–74 years; median 41.6 years) with biopsy-proven lymphoma, 147 thoracic PET scans were retrospectively reviewed. Forty-five of our patients suffered from Hodgkin's disease (HD); 19 patients showed histological subtype nodular sclerosis, 17 mixed cellularity, 6 patients with lymphocyte depleted subtype and 3 were unclassifiable. Of the 43 patients with non-Hodgkin's lymphoma (NHL), 3 had low-grade disease, 4 intermediate-grade, and 36 high-grade disease according to the Working Formulation (38). One patient was not classifiable as having the diagnosis HD or NHL. Patients were treated with standard chemotherapy. Patients with bulky disease additionally underwent radiotherapy. In 58 out of 89 patients PET was performed in addition to treatment. In these patients follow-up time was 36 months (mean), with a range of 12 to 72 months. Two of these patients were lost to follow-up 2 and 24 months after completion of therapy; 17 patients were in progressive disease stage or died after treatment, with a mean follow-up time of 9 months. All patients or guardians gave informed consent before enrolment in the study.

FDG-PET IMAGING

FDG-PET studies were carried out using a Siemens-CTI-ECAT Scanner 931/08/12 (Knoxville, TN). Since October 1995, we used a Siemens-ECAT-Exact HR + Scanner. Static emission scans were obtained in all patients from the neck to the lower pelvis. Six to eight bed positions were obtained 50–60 min after FDG administration. Transmission scans for attenuation correction were acquired using a germanium-68/gallium-68 ring source before FDG administration. This 8-ring system produces 15 simultaneous image planes per bed position with an interplane distance of 6.75 mm. Transmission scans were performed prior to emission scans on the same day. Correct repositioning of the patients was assured by multiple laser-guided landmarks. Acquisition time for emission scanning was 15 min per bed position. Patients received 270 MBq (range, 250 to 350 MBq) intravenously; 20 mg furosemid (Lasix;

Hoechst, Frankfurt am Main, Germany) was given before scanning to reduce the artifacts attributable to high concentrations of FDG in the renal collecting system. Patients were fasted for at least 6 to 8 h prior to PET scans. Image reconstruction was performed by an iterative reconstruction algorithm (39). Actual resolution was 7 mm for iterative reconstruction for full with at-half maximum at the center of the field of view. The qualitative evaluation of the PET results on black and white x-ray films was performed blind and independently on transversal, coronal and sagittal slices by two nuclear medicine physicians (J.K., S.N.R.). In individual cases, additional evaluation on the monitor was performed with alteration on the gray scale. Any clearly delineated uptake in the hilar and mediastinal regions was considered as suspected lymphoma. Both investigators were blinded to the clinical status of the patients as well as to the interpretation of the other investigator. The final PET result was determined by consensus of both investigators.

FDG-PET was routinely performed before treatment in 89 patients. In addition, in 58 of these 89 patients FDG-PET was performed after completion of therapy in order to assess patient response. Baseline FDG-PET was carried out within two weeks (mean) of CT. Follow-up FDG-PET was performed at least 8 weeks after completion of treatment, to eliminate the possibility that partly treated lymphoma evolving toward resolution might be miscategorized as a false-positive lesion.

The uptake of FDG-PET was diagnosed as malignant, based on positive CT scans before and after treatment and clinical follow-up evaluation.

The lesion hilar or mediastinal was considered to be false-positive if there was FDG uptake at baseline study and follow-up study without corresponding findings at CT and if there was FDG uptake after treatment in a lesion seen at CT and if the patient remained in complete remission.

A quantitative analysis of FDG uptake was not performed (40).

CT TECHNIQUE

Computed tomography examinations of the thorax were performed with a conventional CT scanner (CT-Pace; GE Medical systems, Milwaukee, Wis). Section thickness was 10 mm in the chest. Non-ionic contrast material was injected intravenously (200 ml iopamidol (612 mg iodine per milliliter), Solutrast 300; Byk Gulden, Constance, Germany). Any lymph node greater than 10 mm was considered to be involved by lymphoma. Results of the CT scans were evaluated by investigators without knowledge of the clinical and PET data.

Statistical analysis

Sensitivity, specificity, positive predictive value and negative predictive value were calculated by standard methods.

RESULTS

In 89 out of 147 (60%) reviewed PET scans, there was no FDG uptake in the hilar or mediastinal regions; 58 out of 147 (40%) PET studies did, however, show FDG uptake in the hilar or mediastinal regions. In 52 of the 58 abnormal studies (90%) uptake was at sites of lymphomatous lesions, confirmed as true-positive by CT scans and follow-up examinations. Forty-six of the positive studies indicating sites of lymphoma were baseline studies, two were sites of non-responding disease, and four were sites of recurrence. In 6 of the 58 abnormal studies (10%) FDG uptake was false-positive, without any sign of active lymphoma. Four of these six studies were baseline PET studies and two were follow-up studies. In the two patients with false-positive FDG uptake after treatment, CT follow-up studies showed residual tumor masses without any sign of active lymphoma in either patient. Neither of these two patients underwent radiation therapy as part of the therapy to locally control bulky disease. In both patients CT scans showed thymus hyperplasia, one case proven by guided biopsy.

There were two false-negative results of FDG-PET: in one patient with high-grade lymphoma, lymphomatous involvement of the hilar region was negative on baseline study and in the second patient with Hodgkin's disease, PET was negative at the site of residual mass. The 26-year-old woman with Hodgkin's disease relapsed 15 months after negative PET. The results of our study are summarized in Table 1.

Fig. 1 illustrates the PET finding in a patient with false-positive FDG uptake at baseline study. Fig. 2 shows the false-positive FDG uptake in a patient after treatment, which was considered as thymus hyperplasia.

Sensitivity of FDG-PET was 96%, specificity 94%, positive predictive value 90% and negative predictive value 98%, respectively.

DISCUSSION

In this study we examine the role of FDG-PET in predicting lymphomatous involvement in the hilar and mediastinal regions. False-positive FDG uptake without signs of

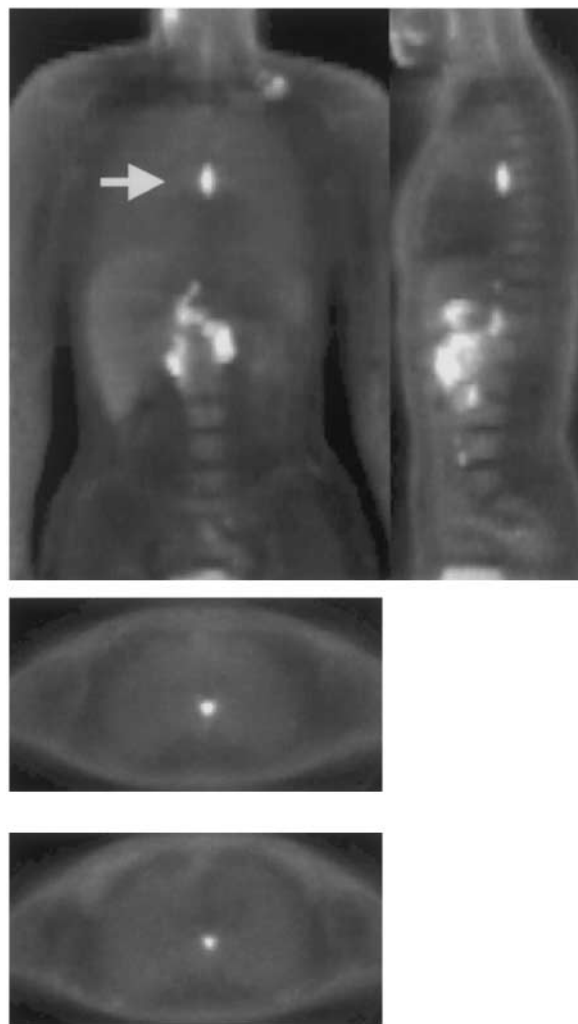


Fig. 1. Coronal (A) and transverse (B) PET scans in a patient with NHL before treatment. Focally increased FDG accumulation (arrowhead) in the hilar lymph node region. On contrast CT, this lesion was not depicted, and FDG uptake was considered as false-positive.

active lymphoma occurred in 6 out of 147 PET studies. The pattern of hilar and mediastinal involvement in patients with lymphoma is variable. In HD, contiguous involvement of the hilar and mediastinal regions is common; in NHL, such contiguity is often absent and hilar lymph nodes may be involved separately (41). Identification of hilar uptake poses a diagnostic dilemma, especially in monitoring patients with residual masses in the mediastinum. False-positive hilar uptake is a common finding, when the Ga-67 SPECT technique is used (13–15). The reason for this phenomenon is presently unknown. In 59 out of 107 studies evaluated by Even-Sapir et al. (15), the hilar uptake was not associated with lymphoma.

It is well known that an overlap exists between FDG uptake in malignant lesions and benign lesions. However, to date, only a few studies have investigated the role of FDG-PET in the differentiation of benign from malignant

Table 1

Results of FDG-PET before and after treatment in 89 lymphoma patients

	Baseline studies (n = 89)	Follow-up studies (n = 58)
PET-positive n = 58	50 (46 true-positive) (4 false-positive)	8 (6 true-positive) (2 false-positive)
PET negative n = 89	39 (38 true-negative) (1 false-negative)	50 (49 true negative) (1 false-negative)

uptake. False-positive FDG-PET uptake has been seen in thymus hyperplasia, tuberculosis, granulomatous lesions, necrosis or inflammatory lesions (31–37).

In the present review of 147 PET studies in 89 consecutive lymphoma patients, 6 patients had false-positive FDG uptake in the hilar and mediastinal regions. In our series, false-positive uptake was found during examinations both before treatment and after treatment. None of these patients had a history of acute or chronic cardiopulmonary disease and none of the patients was a smoker. All patients with false-positive FDG uptake suffered from NHL. False-positive FDG uptake after treatment was at the site of thymus hyperplasia in each of the two patients. Thymus hyperplasia is a common phenomenon in patients after treatment (42). The incidence is reported to be up to 16%, especially in children. One case of false-positive FDG-PET in a child with HD on account of thymus hyperplasia after treatment has been reported up until now (34). The mediastinal mass was found four months after discontinuing therapy.

The significance of semiquantitative measurement of FDG uptake remains controversial. Some investigators

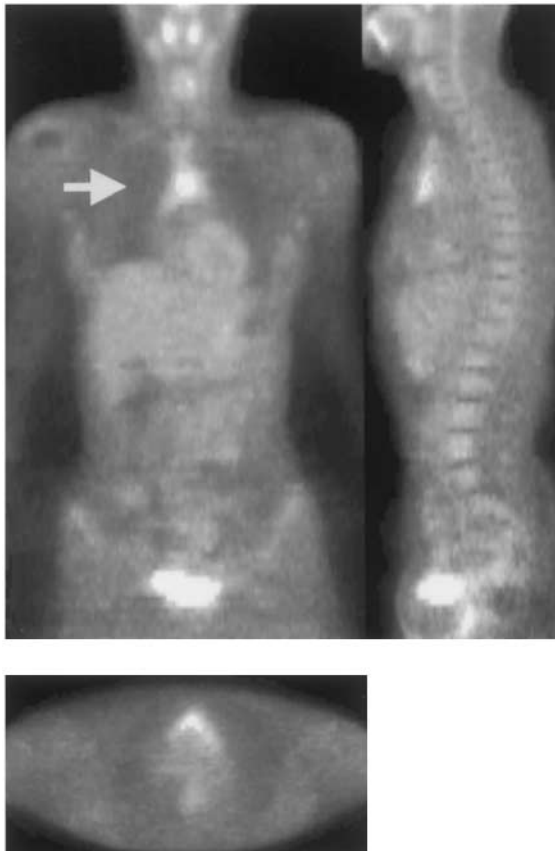


Fig. 2. A 24-year-old female with NHL or HD in complete remission 5 years after end of chemotherapy. Coronal (A) and transversal (B) FDG-PET scans demonstrate false-positive FDG uptake in the mediastinal region (arrowhead), which was considered to be thymus hyperplasia on account of radiological findings.

Fig. 3. An example of unspecific symmetric FDG uptake at both sites of the neck in a patient with HD. This phenomenon occurred after radiotherapy and was not evident in the next PET examination two months later.

have shown that quantitative measurement of FDG uptake, such as standard uptake value (SUV), may help in differentiating malignant from benign lesions (24, 43, 44). Hoffmann et al. (44) were able to show a significant difference in semiquantitative FDG uptake in patients with AIDS or acquired immunodeficiency syndrome with cerebral lymphoma and inflammatory processes. In the study by Inoue et al. (31), false-positive FDG-PET results were reduced by analysis of uptake shape and serial changes in SUV. However, measurement of FDG uptake by semiquantitative techniques, such as SUV, is affected by many factors such as plasma glucose levels, size and placement of the region of interest, size of patients and partial volume effects (40). We agree with the data of Lowe et al. (45) who studied the difference between malignant and benign focal pulmonary lesions. Their data confirm that there may be no substantial difference between visual analysis of focal pulmonary lesions and semiquantitative measurement with SUV.

We did not see symmetric false-positive uptake in the mediastinal and hilar regions as it sometimes occurs when Ga-67 scintigraphy is performed. We have observed these unspecific, false-positive FDG uptakes as symmetric 'bead-on-a-string-like' changes at the location of cervical and clavicular lymph nodes (Fig. 3).

Our data suggest that visual evaluation of FDG uptake in hilar and mediastinal regions is sufficiently high. We cannot explain the false-positive FDG uptake at baseline PET studies. However, the fraction of false-positive studies at baseline PET studies in our study was relatively small (4%). A limitation of this study is that these PET results were not confirmed by biopsy. However, invasive diagnostics, especially in the hilar and mediastinal regions, represent increased risk for the patients. In our study dealing with FDG-PET in the nodal staging of lymphoma (20), we were able to show that PET is more accurate in staging

than CT. It can be supposed that some of the false-positive PET results are probably true-positive. Usually lymph nodes smaller than 10 mm are not regarded as being involved (46). However, some studies dealing with lymphoma could show that normally sized lymph nodes are involved, too (47).

Two of the main trends in healthcare at the present time are: increasing cost-effectiveness and decreasing the number of invasive procedures. Non-invasive, metabolic imaging methods, such as FDG-PET, could allow significant reduction in the utilization of more costly and invasive surgical methods for exact staging and treatment monitoring in patients with lymphoma. However, at the moment FDG-PET is an expensive non-invasive imaging method, which may reduce its acceptability compared to other imaging methods.

Visual FDG-PET analysis appears to be a reliable non-invasive imaging method in predicting lymphoma in the hilar and mediastinal regions. False-positive FDG uptake in the hilar and mediastinal occurred only in a small number of patients in our study. Further studies comparing FDG-PET and Ga-67 scintigraphy are needed to confirm these data.

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