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Whole-body ^{18}F-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma

G. JERUSALEM,* V. WARLAND, F. NAJJAR, P. PAULUS, M.F. FASSOTTE, G. FILLET and P. RIGO

Divisions of Onco-haematology and Nuclear Medicine, University Hospital, Liege, Belgium

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Summary

Whole-body metabolic information provided by ^{18}F-FDG PET could help in the evaluation of lymphoma patients at diagnosis and follow-up. We studied 60 patients, 42 at initial presentation and 18 for disease recurrence (23 aggressive non-Hodgkin's lymphoma, 21 low-grade non-Hodgkin's lymphoma and 16 Hodgkin's disease). All patients underwent a clinical examination, computed tomography (CT) and a non-attenuated PET scan within 1 week. The patients received 222–296 MBq (6–8 mCi) ^{18}F-FDG intravenously and emission scans were recorded 45–90 min later. ^{18}F-FDG PET detected more lymph nodes than the clinical examination or CT, but this rarely resulted in upstaging (two patients). The concordance between PET and CT for the evaluation of the spleen, liver and digestive tract was quite good. Discordance was noted in 12 patients for the evaluation of bone marrow infiltration, but confirmation by MRI or focal biopsy was not always obtained. We conclude that non-attenuated ^{18}F-FDG PET is an easy and efficient whole-body method for the evaluation of patients with lymphomas. Compared with conventional techniques, however, it does not appear to offer much improvement for staging but provides a satisfactory base for follow-up. (© 1999 Lippincott Williams & Wilkins)

Introduction

Positron emission tomography (PET) provides high-resolution images using radiopharmaceutical-labelled positron emitters. It was used initially in neurology and cardiology, but recent improvements in whole-body PET scanning technology have resulted in an increased number of studies and applications in the field of oncology.

More than 60 years ago, Warburg *et al.* [1] observed that malignant tissue is characterized by an enhanced rate of glycolysis in the presence of oxygen. Increased glycolysis is one of the most distinctive biochemical features of malignant cells and results from amplification of the glucose transporter protein at the tumor cell surface as well as from increased activity of hexokinase [2].

PET studies of cancer with the glucose analogue 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (^{18}F-FDG) are widely used for diagnostic staging and evaluation of treatment responses in a variety of neoplasms [3–5]. Like glucose, ^{18}F-FDG is transported into cells by a glucose transporter protein where it is rapidly converted into ^{18}F-FDG-6-phosphate. As the latter is not a substrate for G6P isomerase, it is biochemically trapped in metabolizing tissue.

Preliminary results suggest that ^{18}F-FDG-PET is a useful tool for staging and monitoring lymphoma [6–17]. Indeed, it can detect both nodal and extranodal sites of disease, reveal the activity or lack of activity of residual masses and provide evidence of recurrence [15]. A number of techniques have been used to image lymphoma but none has been entirely satisfactory [6–19]. At present, a clinical examination and computed tomography (CT) are used both for initial staging and follow-up in lymphoma [20]. Metabolic imaging using biological tracers provides different but complementary information to that obtained by anatomical imaging techniques. Previous studies have documented the ability of ^{18}F-FDG-PET to image lymphoma involvement within lymph

*Address all correspondence to G. Jerusalem, Onco-haematology, C.H.U. Sart Tilman, B.35, B-4000 Liege 1, Belgium. e-mail: prigo @chu.ulg.ac.be

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nodes of normal size. The aim of this study was to provide more global information on the potential of ^{18}F-FDG to image both nodal and extranodal sites of the disease and to serve as an accurate baseline for therapeutic follow-up.

Materials and methods

From June 1994 until February 1996, 60 patients (age 18–80 years) with histologically proven lymphoma were enrolled into the study. Twenty-three patients had aggressive non-Hodgkin's lymphoma (NHL), 21 patients had low-grade NHL and 16 patients had Hodgkin's disease. Forty-two patients (18 aggressive NHL, 11 low-grade NHL and 13 Hodgkin's disease) were evaluated at initial presentation; 18 patients (5 aggressive NHL, 10 low-grade NHL and 3 Hodgkin's disease) underwent PET for disease recurrence. In this comparative study, all patients were submitted to a clinical examination, CT and a PET study within 1 week.

Whole-body PET using ^{18}F-FDG was performed with a UGM Penn PET scanner. All patients received 222–296 MBq (6–8 mCi) ^{18}F-FDG intravenously and emission scans were recorded 45–90 min later. The patients were asked to fast for at least 6 h prior to the study. A whole-body acquisition was performed from the cervical region to the inguinal region. It consisted of 10–12 separate overlapping acquisitions, each covering 12.8 cm and each performed over 4 min. Subsequent acquisitions were performed after a 6.4-cm displacement of the table. The total image acquisition time was about 50 min. The images were reconstructed using filtered back-projection and a Hanning filter and reoriented in the transverse, coronal and sagittal planes. A 4 × 4 mm voxel matrix size was used. The isotropic three-dimensional resolution was better than 8 mm. Attenuation correction was not performed. All PET images were reviewed blindly by one investigator (G.J.). The initial PET interpretation was qualitative. Any focus of increased ^{18}F-FDG uptake over background not located in areas of normal ^{18}F-FDG uptake and/or excretion was considered positive for tumour. Furosemide (20 mg as a slow intravenous injection) was administered to patients with suspected pelvic abnormalities to provide ^{18}F-FDG bladder elimination. These patients were studied 60–90 min later and after voiding. Diazepam (5 mg) was given orally before ^{18}F-FDG administration in some tense patients to prevent muscular uptake.

Intravenous contrast enhancement was performed in every CT examination. The chest, abdomen and pelvis were systematically investigated. Standard CT size criteria were used to discriminate pathological lymph nodes. The cervical, axillary and inguinal regions were explored clinically. In the clinical examinations, lymph nodes with a minimum diameter of 10 mm were arbitrarily suspected of being infiltrated by lymphoma.

We examined the concordance between the PET images and the presence of masses or enlarged lymph nodes after clinical examination and after CT. In cases of discordance, the CT images were reanalysed. The response to treatment and follow-up were used to assess the overall accuracy of the patient evaluation. Biopsy was performed for histological diagnosis but, for ethical reasons, a systematic biopsy of the various lesion sites was not performed for staging, except when considered clinically necessary.

Results

Lymph nodes

Peripheral lymph nodes. Clinically undetected peripheral lymph nodes were demonstrated to be hyperactive by ^{18}F-FDG PET in 12 patients (9 at initial presentation, 3 with disease recurrence). Clinically detected lymph nodes showed increased uptake in 7 patients (3 at initial presentation, 4 with disease recurrence). The clinical and ^{18}F-FDG PET results were concordant in 41 patients.

Intrathoracic and intra-abdominal lymph nodes. Additional lymph nodes were observed with ^{18}F-FDG-PET in 5 patients (3 at initial presentation, 2 with disease recurrence). Lymph nodes of increased size were detected by CT but not by ^{18}F-FDG PET in 8 patients (6 at initial presentation, 2 with disease recurrence). Two patients were not evaluable because CT studies were not performed. The two techniques identified the same lesions in 45 patients.

Overall results. Additional lymph nodes were observed with ^{18}F-FDG PET in 15 patients (10 at initial presentation: 8 aggressive NHL, 2 Hodgkin's disease; 5 with disease recurrence: 2 aggressive NHL, 3 low-grade NHL). More lesions were identified by clinical examination or CT in 11 patients (7 at initial presentation: 5 low-grade NHL, 2 Hodgkin's disease; 4 with disease recurrence: 1 aggressive NHL, 2 low-grade NHL, 1 Hodgkin's disease). We observed upstaging by ^{18}F-FDG PET in two patients: one Hodgkin's disease stage IA to stage IIA at initial presentation (same treatment: radiotherapy) and one low-grade NHL stage II to stage III with disease recurrence (same treatment: systemic chemotherapy). In 34 patients, ^{18}F-FDG PET and the conventional evaluation detected similar lymph node extension of the lesion (Figs 1 and 2).

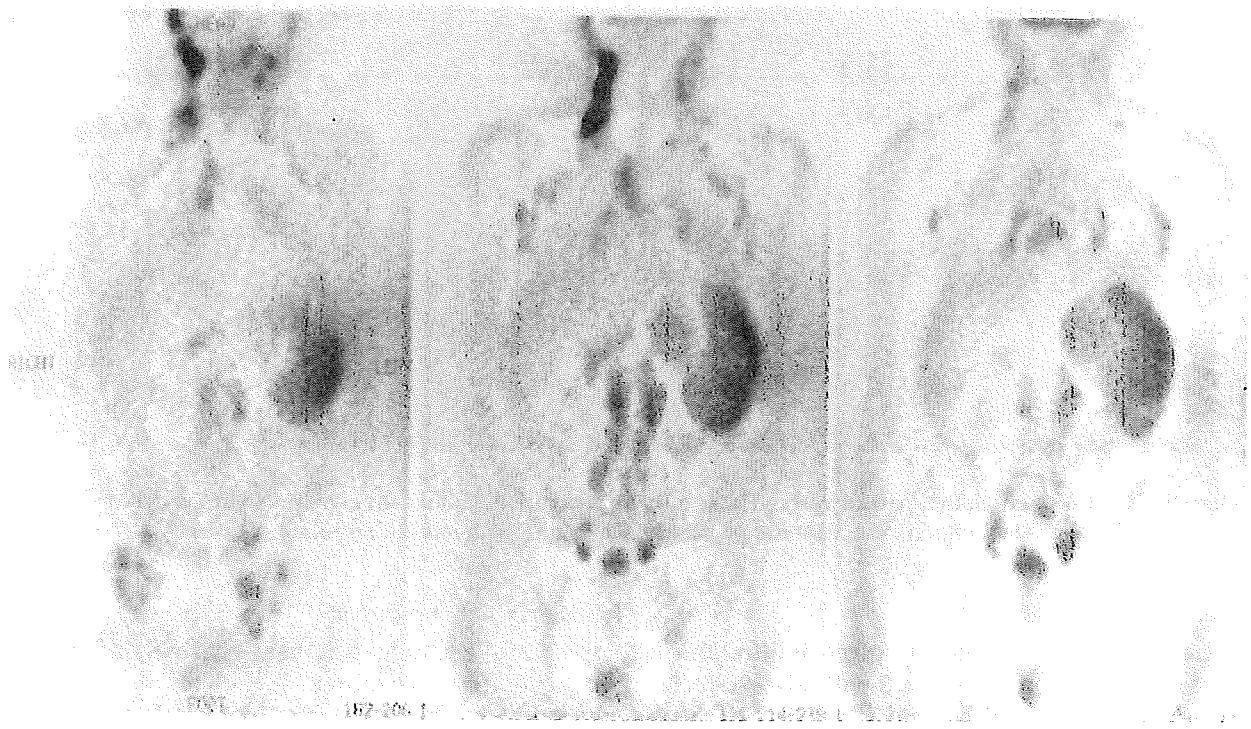

Fig. 1. Whole-body ^{18}F-FDG PET scan in a patient with high-grade NHL. Three coronal slices at various levels demonstrate nodal uptake in the cervical, axillary and inguinal regions as well as in the mediastinum and the periaortic regions. The spleen is also enlarged and demonstrates increased uptake.

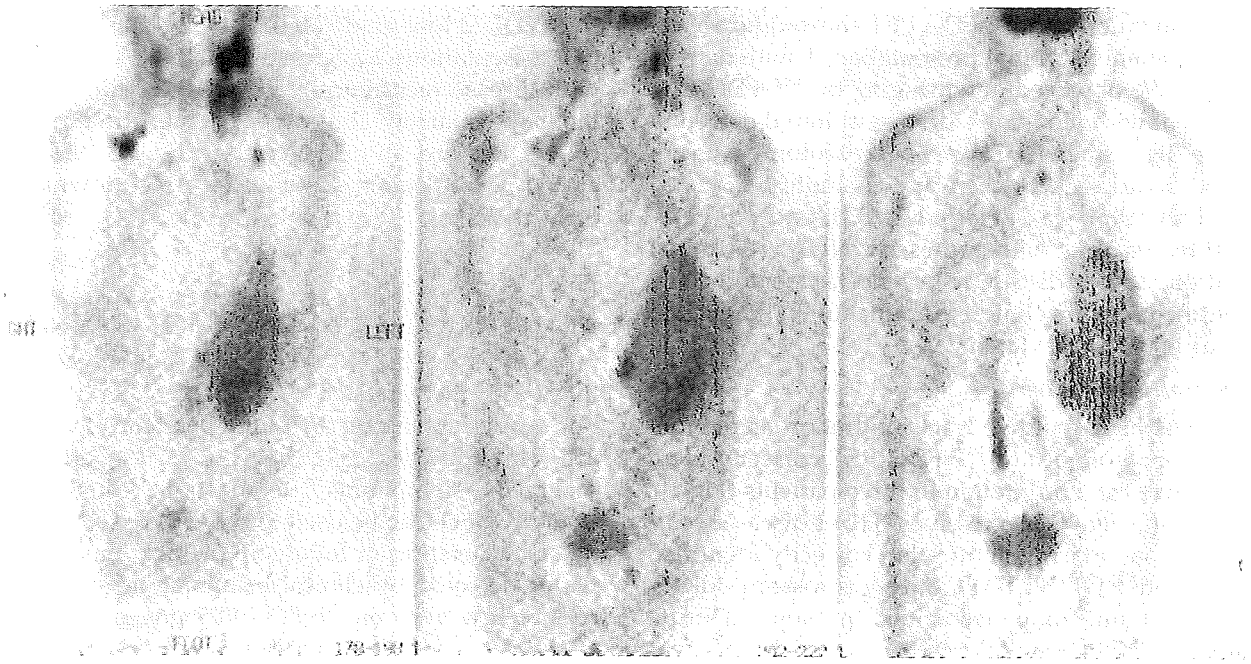

Fig. 2. Whole-body ^{18}F-FDG PET scan in a patient with low-grade lymphoma. Nodal uptake is present in the cervical and subclavicular regions. Mild uptake is also present in the mediastinum. A markedly enlarged spleen can also be visualized. The linear uptake in the abdominal region corresponds to the ureters.

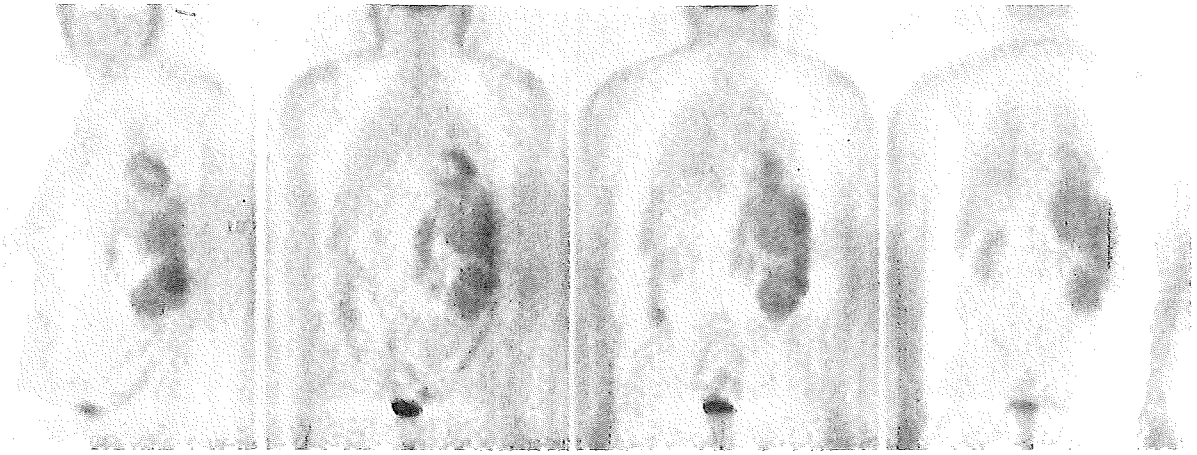

Fig. 3. Digestive tract infiltration in a patient with NHL at initial presentation. Uptake involves much of the descending colon and omentum in the left peritoneal region. Visualization of part of the brain, the heart, kidneys and bladder is as normal.

Spleen and liver

There were concordant results for spleen infiltration in 11 patients (8 at initial presentation, 3 with disease recurrence). Computed tomography and ^{18}F-FDG PET both indicated lymphomatous infiltration of the spleen in four patients, but no splenomegaly was noted at clinical evaluation. PET showed increased splenic ^{18}F-FDG uptake in one patient (disease recurrence) without detection of splenomegaly by CT or by clinical examination. In three patients, CT showed splenomegaly while the clinical examination and ^{18}F-FDG PET showed no abnormalities (2 patients at initial presentation, 1 with disease recurrence). We observed downstaging by ^{18}F-FDG PET in one patient with Hodgkin's disease at initial presentation (stage IIIs→ stage II). However, laparotomy was not performed because chemotherapy was indicated.

Liver infiltration was detected by CT and ^{18}F-FDG-PET in three patients with aggressive NHL (1 at initial presentation, 2 with disease recurrence). Hepatomegaly was identified only on clinical examination in the patient studied at initial presentation.

Digestive tract infiltration

Four patients had digestive tract infiltration as demonstrated histopathologically. ^{18}F-FDG PET correctly identified digestive tract infiltration in three patients (Fig. 3). In one patient (stage IV aggressive NHL at disease recurrence, with bone marrow infiltration correctly identified by biopsy and ^{18}F-FDG PET), only gastroscopy identified the gastric infiltration confirmed by biopsy. Diffuse physiological ^{18}F-FDG uptake in the digestive tract was observed in some patients. A differential diagnosis between physiological ^{18}F-FDG uptake and tumour infiltration is usually based on three-dimensional examination of the data and on the tubular pattern of non-pathological ^{18}F-FDG uptake in the digestive tract.

Bone marrow infiltration

^{18}F-FDG PET suggested bone marrow infiltration in 18 patients. This was focal in 16 patients and diffuse (homogeneous) in 2 patients (Figs 4 and 5). Bone marrow infiltration was confirmed by biopsy in 13 patients (10 at initial presentation, 3 with recurrence). Bone marrow biopsy was negative in four patients (2 aggressive NHL and 2 Hodgkin's disease, all at initial presentation). Bone marrow biopsy was not performed in the fifth patient (recurrent aggressive NHL). In eight patients (2 aggressive NHL, 2 low-grade NHL, 1 Hodgkin's disease at initial presentation; 2 aggressive NHL, 1 low-grade NHL with disease recurrence), ^{18}F-FDG PET did not identify the bone marrow infiltration demonstrated histologically. Therefore, an upstaging by ^{18}F-FDG PET was suggested in five patients and an incorrect downstaging in eight patients.

Discussion

^{18}F-FDG PET is an alternative to conventional imaging procedures in patients with malignant disease. Indeed, the use of increased ^{18}F-FDG metabolism as an indication of disease makes PET independent of morphological abnormalities. As reported by several authors, malignant lymphoma demonstrates high ^{18}F-FDG uptake, which can be used to show disease involvement, detect recurrences or follow up therapy. Enlarged lymph nodes detected by clinical examination or CT without metabolic activity on ^{18}F-FDG PET images are not necessarily false-negative. Indeed, these enlarged lymph nodes may be reactive rather than infiltrated by lymphoma. On the other hand, normal-sized lymph nodes may be infiltrated by lymphoma. Many studies have relied on a limited segmental assessment of patients or have reported whole-body evaluation but limited their

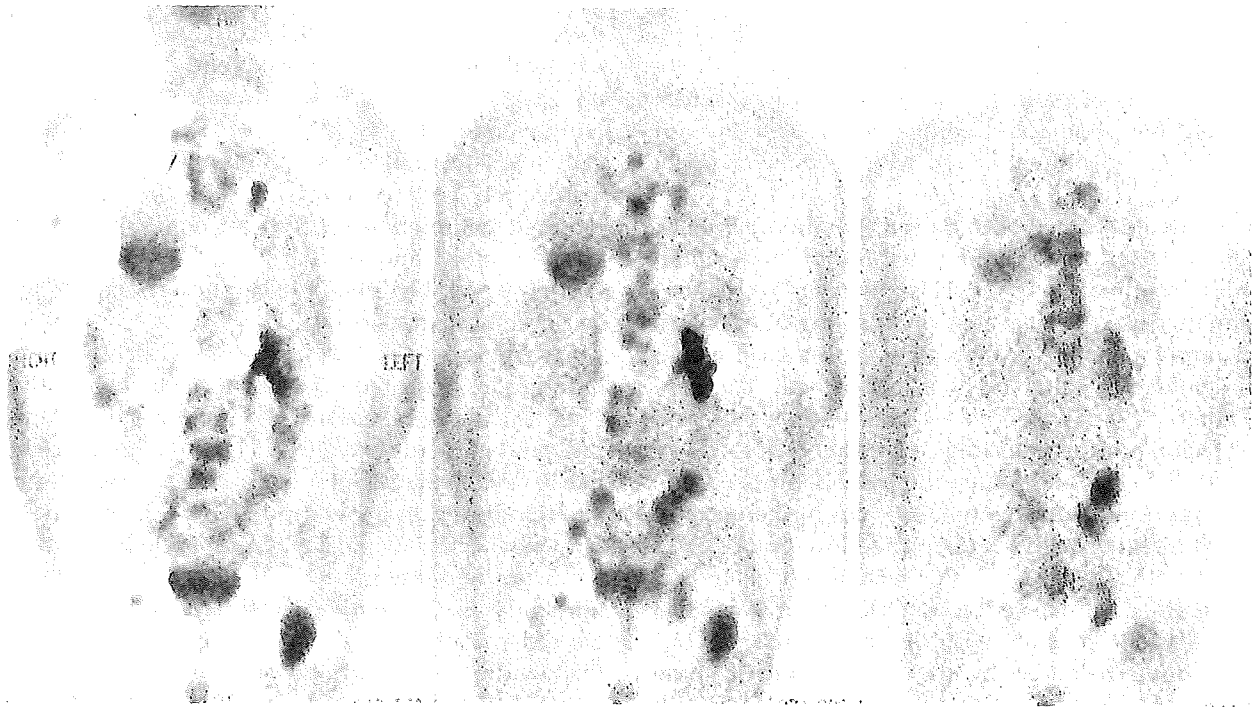

Fig. 4. Multiple focal bone marrow involvement in a patient with a recurrent high-grade lymphoma. Activity in the spine is both heterogeneous and intense. Bone marrow activity is also present in the sacroiliac and left femoral regions. Nodal involvement in the mediastinum, focal liver uptake and a dilated left kidney can also be seen.

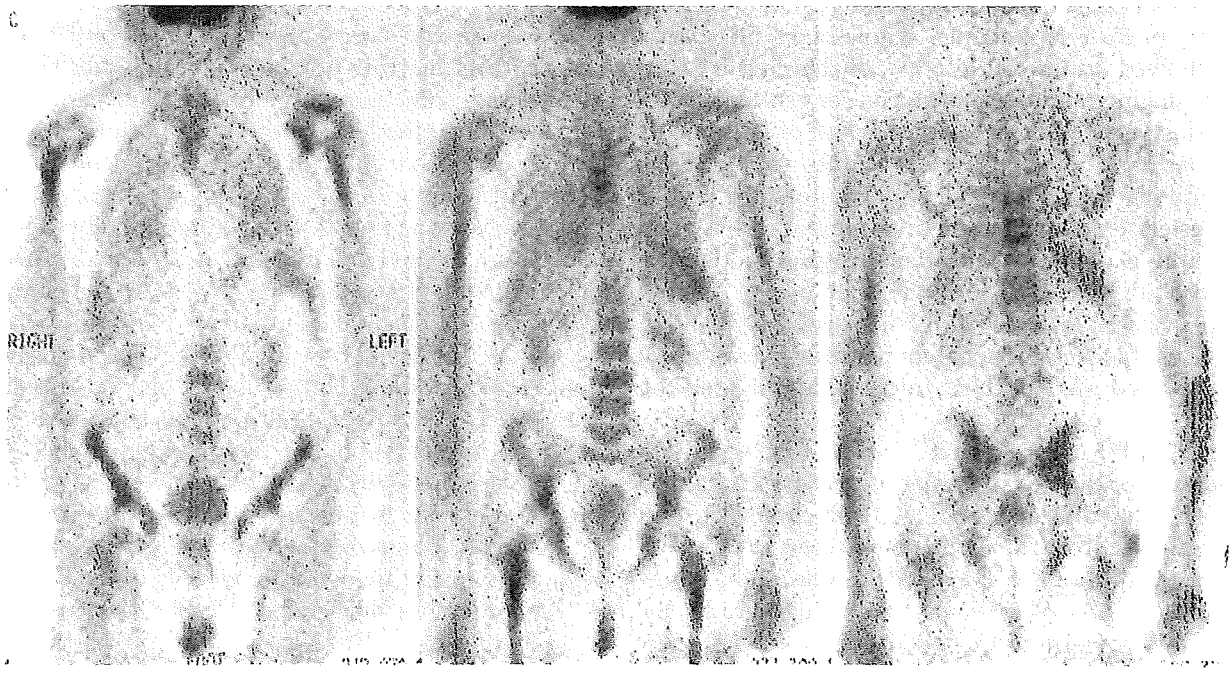

Fig. 5. Diffuse bone marrow uptake in a patient receiving chemotherapy and marrow growth factors. The axial skeleton, scapula, pelvis and the proximal part of the peripheral bones can be visualized.

analysis primarily to lymph node extension. In this preliminary study, we performed comprehensive whole-body evaluations of patients with biopsy-proven initial or recurrent lymphoma and compared the results with clinical and CT examinations as well as bone marrow biopsy.

In the patients studied at initial presentation, ^{18}F-FDG PET demonstrated more hyperactive lymph nodes than the clinical examination or CT. This, however, corresponded to an increased clinical stage in one patient only and did not imply a change in therapy. A histological examination could not, therefore, be performed. We confirmed that ^{18}F-FDG PET is a highly sensitive and reliable technique for detecting aggressive NHL. Compared with the clinical examination, we only missed one axillary lymph node approximately 1 cm in diameter in a patient presenting with a transformed low-grade NHL. Compared with CT, ^{18}F-FDG PET visualized all lymph nodes identified. Enhanced lesion detection was also observed in some patients with disease recurrence, but this was counterbalanced by the observation of some probable false-negative nodes, mainly in patients with low-grade NHL.

Hoh *et al.* [8] reported that a whole-body ^{18}F-FDG-PET-based staging algorithm may be an accurate and cost-effective method for staging and restaging Hodgkin's disease and NHL. Accurate staging was achieved in 17 of 18 patients (7 Hodgkin's disease, 11 NHL) compared to 15 of 18 patients using a conventional staging algorithm. In 5 of 18 patients, whole-body PET-based staging showed additional lesions not detected by conventional staging modalities, whereas conventional staging demonstrated additional lesions in 4 of 18 patients not detected by whole-body PET. Accurate staging of the entire body in a single imaging study is possible. Hoh *et al.* suggested that, even though a single whole-body scan is more expensive than other imaging modalities, whole-body PET may reduce the cost of the staging work-up in patients with Hodgkin's disease and NHL by targeting the selection of confirmatory anatomical imaging procedures to those regions highlighted by PET.

Moog *et al.* [7] reported that ^{18}F-FDG PET is an efficient method for the nodal staging of primary Hodgkin's disease (27 patients) and NHL (33 patients). PET not only identified all nodal involvement seen on CT, but also showed additional lesions and resulted in a change in staging in 8% of patients. Both high-grade (22 patients) and low-grade (5 patients) lymphomas were detected. There were no false-negative PET findings; therefore, PET never resulted in a lower staging of disease compared with CT. Two false-positive PET findings were found (non-specific inflammatory lymph node changes). Seven of nine histopathologically confirmed diseased lymph nodes detected on PET were macroscopically normal and consequently classified as being not suspicious on CT. In contrast, the three enlarged lymph nodes that were free of disease histopathologically were classified as lymphomatous by CT. These results are very encouraging but the study protocol required completion of both an emission scan (90–120 min duration) and of a full transmission scan (60–80 min). It would be difficult to duplicate such a long protocol in clinical practice.

Rodriguez *et al.* [12] investigated 23 patients with high-grade, low-grade or transformed low-grade NHL. They calculated standardized uptake values, transport rates and mass influx values. The three transformed low-grade NHL behaved in a manner that was intermediate to high-grade and low-grade NHL. This may explain why we missed an axillary lymph node in a patient with a transformed low-grade NHL. The technical features of our study also have to be considered. Like Hoh *et al.* [8], we did not perform attenuation correction or quantitative studies to avoid the substantial prolongation of acquisition time required for whole-body imaging.

Schönberger *et al.* [9], who performed attenuation correction, reported that PET identified additional lesions leading to upstaging in 4 of 17 patients. These additional lesions were mainly found in the abdomen. Furthermore, extranodal involvement of the liver, spleen, bone marrow, lungs and breasts, all histologically verified, was also demonstrated by ^{18}F-FDG PET.

Bone marrow uptake can be observed on ^{18}F-FDG PET scans. Faint marrow uptake is normally observed in the spine and sometimes in the sacroiliac bones. Marked uptake above the level of the liver, peripheral uptake in the femoral and humeral bones and in the thorax, and heterogeneous focal uptake usually represent abnormal bone marrow activity. Diffuse uptake, likely to represent activation of the bone marrow, is observed primarily in patients with bone marrow recovery after chemotherapy and in particular in patients treated with growth factors (such as G-CSF), but can also be observed in some untreated patients. Diffuse bone marrow uptake was observed in only two of our patients studied at the time of initial presentation, one with Hodgkin's disease but a negative biopsy, the other with low-grade NHL and a positive biopsy. In treated patients with diffuse uptake, differential diagnosis between reactive marrow and homogeneously involved marrow is difficult (Fig. 5).

Discordant results between ^{18}F-FDG and bone marrow histology were observed in 13 of 60 patients in this study. Although not ideal, these results are comparable to those of Barrington *et al.* [21]. They observed discordance in 10 of 49 patients; 13 of the remaining 39 patients showed good concordance. It should be noted that, in both studies, areas of positive PET discordant findings

were usually not the site of the biopsy. Biopsy confirmation of these positive PET discordant sites or a comparison with the results of MRI is recommended.

^{18}F-FDG PET appears accurate for the detection of visceral involvement (spleen, liver and digestive tract). Discrepancies between PET, CT and a clinical examination are rare in the evaluation of splenic involvement, but a definitive assessment of the value of PET will require splenectomy and a histological examination, which were not performed in discordant cases in this study as they would not have resulted in a change in treatment. Liver involvement is less frequent and was only observed in two of our cases. Few studies have reported liver and spleen involvement [9].

Digestive tract infiltration was evident in three of four patients (Fig. 3). Diffuse infiltration of the bowel and the peritoneal mesentery is not difficult to differentiate from normal digestive tract uptake. Indeed, this usually predominates in the colon and involves the wall, whereas the intestinal lumen can usually be visualized and followed in space using three-dimensional viewing software (rotating views and thick slices). Normal and abnormal uptake in the stomach is more difficult to differentiate. Normal uptake is usually mild and predominates in the lesser curve of the stomach, whereas abnormal uptake is usually marked and can involve any part of the stomach. In the patient studied, involvement was minimal and not recognized by PET, but this did not result in a change of stage, as this patient was stage IV with bone marrow involvement.

The ability of ^{18}F-FDG PET to detect individual nodal lesions appears lower in low-grade NHL than in aggressive NHL. Leskinen-Kallio *et al.*[11] reported that ^{18}F-FDG uptake is more rapid in high-grade lymphoma and that low-grade lymphoma may not always be visible on PET images. We also found that, in some low-grade lymphomas, additional nodes were identified by CT. In contrast, Newman *et al.* [6] reported high sensitivity for ^{18}F-FDG imaging in low-grade NHL. In their focal quantitative study, the standardized uptake values did not vary substantially between cases of low- and intermediate-grade NHL. Only six patients with low-grade NHL were studied, however, all of whom had received previous chemotherapy (and radiotherapy in two patients). Also, all lesions analysed were greater than 2 cm in diameter. Our results suggest better visualization of low-grade lesions in patients with disease recurrence than in patients at initial presentation. We therefore believe that quantitative (attenuation-corrected) studies of low-grade NHL at initial presentation are warranted before definite conclusions can be drawn.

Lack of attenuation correction may be a confounding factor, but new procedures have been devised to facilitate its application. One such procedure available in our laboratory is the use of caesium-137 (^{137}Cs) in singles mode for transmission data acquisition [22]. The choice of a singles source allows a larger activity to be used without detector saturation (as the detector proximal to the source is shielded and not used). This has resulted in a 10-fold decrease in the time necessary for adequate transmission acquisitions. Independently or additionally, segmentation of the transmission image can also be used to reduce the acquisition time and reduce noise, therefore facilitating the routine application of attenuation correction and quantification.

While routine attenuation correction and quantification should be used to improve the diagnostic sensitivity of low-grade lesions, it may also be of some help in differentiating tumour uptake from the non-specific uptake reported with ^{18}F-FDG in infection and inflammation. Although the proper selection of patients and the use of correlative data are necessary for such a differentiation, the use of quantitative ^{18}F-FDG results will also be of value.

The aim of this study was to compare information provided by non-attenuation-corrected whole-body ^{18}F-FDG PET with that available from conventional clinical, imaging and staging techniques. In these conditions, ^{18}F-FDG PET appears to provide comparable data to traditional staging techniques. Although PET detected more lesions at initial presentation, this resulted in few staging changes, thereby probably not warranting the extra cost. Discrepancies between our results and those reported in the literature for patients with low-grade NHL warrant further studies using improved techniques (with attenuation correction).

In the future, ^{18}F-FDG PET is likely to be used to assess the results of therapy and to diagnose the persistence of viable tumours in patients with residual masses [23, 24]. The results of the present study indicate that, although desirable, the acquisition of a pre-therapy baseline study is not mandatory.

In summary, whole-body non-attenuated ^{18}F-FDG PET studies are very sensitive for staging and restaging aggressive NHL. Our results for patients with Hodgkin's disease are encouraging but preliminary.

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