bjh research paper

Positron emission tomography/computed tomography: diagnostic accuracy in lymphoma

Dolores Hernandez-Maraver,[1] Fernando Hernandez-Navarro[1] Nieves Gomez-Leon,[2] Juan Coya,[3] Beatriz Rodriguez-Vigil,[2] Rosario Madero,[4] Immaculada Pinilla,[2] and Luis M. Martin-Curto[3]

Departments of [1]Haematology, [2]Radiology, [3]Nuclear Medicine, and [4]Statistics, La Paz University Hospital, Madrid, Spain

Received 1 April 2006; accepted for publication 17 July 2006

Correspondence: Dr D. Hernandez-Maraver, Haematology Department La Paz University Hospital, Hospital General, Planta 6ª, P° de la Castellana, 261, 28046 Madrid, Spain.
E-mail: hernandezlola@mac.com

Summary

An accurate initial staging of patients with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) is critical for the selection of an appropriate treatment. Computed tomography (CT) remains the standard imaging technique, although it is based on anatomic criteria. Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG) provides useful functional information but requires anatomical correlation to localise lesions accurately. We have prospectively compared the accuracy of combined PET/CT with that of CT and PET alone at initial staging in lymphoma patients. Forty-seven newly diagnosed patients were evaluated. PET/CT was superior compared with CT and PET in nodal evaluation and detection of extranodal disease. Using a staging algorithm with PET/CT resulted in the disease stage being increased in 11 of 47 patients (10 NHL and 1 HL) (McNemar test $P = 0{\cdot}012$). Therefore, a different treatment strategy based on PET/CT findings was suggested for seven patients (14·8%). PET/CT markedly improves accuracy in the diagnostic work-up of patients with lymphoma.

Keywords: PET/CT, lymphoma, Hodgkin, 2-fluoro-2-deoxy-D-glucose positron emission tomography, staging.

Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL) are clonal lymphoproliferative diseases that can present with different clinical manifestations that may be difficult to diagnose (Evans & Hancock, 2003; Re *et al*, 2005). The Ann Arbor (AA) stage (Carbone *et al*, 1971), based on the anatomical extent of the disease, remains the single most important factor influencing relapse-free and overall survival. In addition to clinical history, physical examination and laboratory data, conventional methods for staging HL and NHL may include chest radiograph, computed tomography (CT) or magnetic resonance imaging (MRI), bone scan, gallium scan, lymphangiogram, bone marrow (BM) biopsy and laparotomy. CT scans can depict abnormal anatomy and abnormal contrast enhancement. However, CT has limitations in depicting pathological changes of normal-sized structures, which results in a reduced sensitivity to detect abnormal lymph nodes (Gdeedo *et al*, 1997). Gallium scintigraphy plays an important role in the evaluation of residual tumour mass, because isotope uptake is more intense in viable tumour than in fibrotic tissue. However, to our knowledge, gallium scanning has not been shown to be superior to CT in cases of untreated lymphoma (Ha *et al*, 2000; Bar-Shalom *et al*, 2001). Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG) is an accurate procedure that is based on the observation that cells that underwent malignant transformation are characterised by an elevated glucose metabolism that can be captured by PET (Phelps, 2000; Juweid & Cheson, 2006). Paul (1987) described increased uptake of FDG in lymphoma and the possible display with planar scintigraphy. More recently, several authors have examined the superiority of FDG-PET as compared with CT and Gallium 67 to evaluate nodal involvement by malignant lymphoma (Moog *et al*, 1997; Buchmann & Reske, 2001; Kostakoglu *et al*, 2002; Rini *et al*, 2002; Bar-Shalom *et al*, 2003; Burton *et al*, 2004), its cost-effectiveness for staging of the disease (Hoh *et al*, 1997) and the accuracy of this method to differentiate post-therapeutic scar tissue from viable residual tumour (Buchmann & Reske, 2001; Hutchings *et al*, 2005; Jerusalem *et al*, 2005). The main drawback of PET in tumour imaging is the almost complete absence of anatomic landmarks and lack of specificity because sites of active inflammation also incorporate FDG (Friedberg & Chengazi, 2003; Burton *et al*,

  doi:10.1111/j.1365-2141.2006.06284.x

2004). Recently, a prototype of a combined PET/CT scanner was introduced (Beyer *et al*, 2000; Townsend, 2001; Townsend & Beyer, 2002), that captures PET and CT images coregistered by means of computer hardware in the same imaging session. Combination of both imaging techniques would improve identification and definition of biological abnormalities by PET with the display of the surrounding anatomy by CT (Beyer *et al*, 2000; Townsend, 2001; Townsend & Beyer, 2002). Moreover, the combination of anatomical and biological information produces better definition of the abnormal tissue (Phelps, 2000; Alessio *et al*, 2004; Von Schultess *et al*, 2006). There are only preliminary data suggesting improved diagnostic and staging accuracy and reduction of false positive/negative rates with PET/CT over FDG-PET or CT alone (Hany *et al*, 2002; Schaefer *et al*, 2004; Steinert, 2004). From a clinical perspective, key questions as to whether PET/CT, performed in one session, may replace conventional CT and PET in the initial staging of lymphoma patients remains unanswered. This study prospectively compared the accuracy of lesion detection and clinical staging of whole body PET/CT, either with low dose non-enhanced CT (LD PET/CT) or with contrast-enhanced CT (FD PET/CT) with that of PET alone and the conventional staging work-up of NHL and HL.

Materials and methods

Patients

Forty-seven consecutive patients from the Haematology Department, La Paz University Hospital, Madrid, Spain, were prospectively enrolled onto the study between July 2004 and November 2005. Of the 47 patients, 30 were female and 17 male (mean age, 50 years; range, 23–83 years) and all had untreated biopsy-proven lymphoma. Two patients with recurrent disease who had obtained a complete remission of >3 years without any evidence of residual mass were also included. All patients gave written informed consent to participate in the study in accordance with regulations of the institutional review board. Clinical information is summarised in Table I. Those cases with a previous diagnostic CT were excluded from the study. Biopsy specimens were reviewed and classified by a haematopathologist at La Paz University Hospital according to the World Health Organization classification system (Harris *et al*, 1999). Thirty-one patients had NHL and 16 had HL. All patients underwent conventional staging studies, which included clinical history, physical examination, laboratory work-up (complete blood count, serum creatinine, urea, liver function tests, lactate dehydrogenase (LDH), β2 microglobulin, viral serologies), chest radiograph, biopsy of both the enlarged lymph node and of the iliac crest BM, and PET/CT before institution of therapy. MRI, endoscopy, lumbar puncture or other diagnostic tests were performed if clinically indicated. The clinical stage of the patients was assessed according to the modified AA classification (Lister & Crowther, 1990). Prognostic factors according to the International Prognostic Index (IPI) scores for HL (Hasenclever & Diehl, 1998) and NHL (The International NHL Prognostic factors Project., 1993; Solal-Celigny *et al*, 2004) were also recorded.

Table I. Patient characteristics.

Patients	NHL	HL
n	31	16
M:F	9:22	10:06
Age [years; mean (range)]	59 (15–83)	17 (20–61)
Pathological subtype	Follicular, 2 Burkitt, 1 DLBCL, 17 MCL, 1 MZL, 6 SLL, 1 PTCL, 2 ACL, 1	Nodular sclerosis, 11 Mixed cellularity, 2 Lymphocyte predominant, 3

NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; M, male; F, female DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; PTCL, peripheral T cell lymphoma; ACL, anaplastic cell lymphoma.

Hybrid camera-based PET/CT imaging protocol

All PET/CT scans were performed at the same nuclear medicine/radiology department and interpreted by the same team of specialists. Patients fasted for at least 4 h before the examination. ^{18}FDG was injected intravenously at a dose of 370 MBq and the patient's activity and speech was limited for 45–60 min immediately following injection of the radioisotope. In addition, 1500 ml of oral contrast (Gastrographin 3%) was administered immediately after the injection of ^{18}FDG.

Acquisition of the data

All data were acquired with a combined PET/CT in-line system (Discovery LS; GE Medical Systems, Waukesha, WI, USA) that integrates a four-detector row spiral CT scanner (Light-SPeed Plus; GE Medical Systems) with a PET scanner (Advance Nxi, GE, Medical Systems). Initially, a low-dose non-enhanced CT acquisition was performed with the following parameters: 140 KV, 80 mAs, 0·5 s per gantry rotation, collimator width of 2 ×5 mm, section thickness of 5 mm, reconstruction interval of 3 mm.

A PET emission scan was carried out immediately following the CT acquisition, encompassing the same transverse field of view as the CT images, in a caudocranial direction. Four to six contiguous volumes were acquired, each of 14·6 cm long and with a 4 cm overlap between table stations in a total acquisition time of approximately 16–24 min. The final spatial resolution after reconstruction was 4·8–6·2 mm. Finally, a

diagnostic full-dose contrast enhanced CT study was performed, with the same parameters as low-dose non-enhanced CT except for mAs (300 mAs) and following injection of 140 ml of a low-osmolarity iodinated contrast medium (Iobitridol, 300 mg of iodine/ml) at a rate of 3 ml/s by using a power injector with a scan delay of 45 s. Images were transferred to a workstation (eNTEGRA or XELERIS; GE Medical System) equipped with fusion software that enabled multiplanar reformatted images.

Image evaluation

Two experienced nuclear medicine physicians interpreted the camera-based ^{18}F-FDG PET studies, while CT images were reviewed by two experienced radiologists; all of them were blinded to the other imaging modality. Hybrid images were interpreted together by radiologists and nuclear medicine physicians in consensus. The criteria for interpretation of camera-based ^{18}F-FDG PET studies included the presence of abnormally increased tracer uptake at each suspected site. CT criteria for malignancy included the presence of organomegaly, an abnormal mass or structural changes inside a normal-sized organ. Lymph nodes were considered abnormal by CT if the diameter was >10 mm for cervical and thoracic nodes, >5 mm for abdominal nodes and >10 mm for pelvic nodes (except inguinal nodes >15 mm). Size of lesions was assessed using a two-dimensional method on high-resolution conventional CT. In case of disagreement the final interpretation was determined by a majority opinion for both nuclear medicine physicians and radiologists.

Reference standard

Histological confirmation of all sites suspected of lymphoma involvement using imaging techniques is difficult (Römer & Schwaiger, 1998; Segall, 2001). For this reason, some authors have established the final stage of the disease on the basis of all available data, including PET (Tatsumi *et al*, 2001). This approach may favour the least specific test, as discussed by Segall (2001). The present study summarised the results of all conventional staging procedures: clinical evaluation (which included history, physical examination and laboratory data), contrast-enhanced CT, or other imaging studies (MRI or Gallium scan if necessary), and biopsy, if available. The combined results of clinical and imaging studies and the results of the biopsy formed the basis of our Reference Standard in the staging of NHL and HL, an approach that has also been used to establish the true clinical stage of the disease by others (Hoh *et al*, 1997; Moog *et al*, 1997; Hany *et al*, 2002; Weihrauch *et al*, 2002; Schaefer *et al*, 2004). Moreover, all questionable discrepancies between PET/CT and CT or PET alone, were evaluated during the follow-up after two or three cycles of therapy and after completion of treatment for evidence of regression or progression of the disease. Therefore, the presence of progression or regression indicated, retrospectively, that these areas were involved with lymphoma (confirmation by follow-up).

Data analysis

Lesion detection accuracy was analysed by comparing the results of the PET/CT studies, and PET studies with each other and with the reference standard, as described above, in the following lymph node regions: cervical, thoracic and abdominal-groin. For each group, the number of sites affected was assessed. The following extra nodal sites were evaluated: lung, liver, gastrointestinal and genitourinary tracts, bone, BM and others. The findings for each of these sites were ranked with a grading scale as positive (2), indeterminate (1), or negative (0) for lymphomatous infiltration. To assess the clinical effect of the PET/CT examinations, staging was performed for each patient according the Ann Arbor classification system on the basis of CT, PET images alone and the PET/CT images. Results with this image-based staging were then compared with the true clinical stage as described above.

Treatment protocols

Aggressive NHL. The treatment protocols consisted of three to four courses of R-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, Rituximab) chemotherapy for stage I followed by involved field radiation. Stages II to IV received a full chemotherapy regimen [e.g. either six courses of R-CHOP, three courses of R-ProMACE (Prednisone, Methotrexate, Adriamycin, Cyclophosphamide, Etoposide, Rituximab), eight courses of HyperCVAD (Rituximab/Cyclophosphamide/Mesna/Vincristine/Doxorubicin/Dexamethasone)] and autologous stem cell transplant for patients with an IPI ≥3. *Indolent NHL* patients received three to six courses of Fludarabine-containing regimens + Rituximab, depending on AA stage. In *HL*, treatment for stages I/IIA consisted of three to four courses of ABVD (Adriamicin, Bleomycin, Vinblastine and Dacarbazine) followed by involved field radiation. Therapeutic regimens for advanced stages (IIB, III, IV) were either 6 cycles of ABVD, or 8 cycles of BEACOPP [Bleomycin, Cyclophosphamide, Doxorubicin, Etoposide, Prednisone, Procarbazine, Vincristine] depending on prognostic factors (Hasenclever score ≥3). All patients underwent follow-up PET/CT to assess restaging accuracy and prognostic value of the technique.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Release 9·0; SPSS Inc., Chicago, IL, USA). Quantitative data were described by mean, minimum, and maximum, and qualitative data as counts and percentages. Indeterminate site findings were classified as negative for the analysis of the image-based

staging system. Agreement among techniques was studied by the kappa statistics. McNemar's test was used to analyse symmetry. Differences between techniques for the number of lesions detected were studied by the Wilcoxon signed-rank test. Two-sided tests were used, and a P value less than 0·05 was considered statistically significant.

Results

Region (nodal and extranodal) involvement

Total agreement was found between LD PET/CT and FD PET/CT for the cervical region (Kappa = 1, $P < 0{\cdot}001$). LD PET/CT and FD PET/CT showed almost perfect agreement for the thoracic and abdominal-groin region (FD PET/CT showed no indeterminate findings whereas LD PET/CT had one indeterminate result in each of these regions).

Nodal disease. Cervical. Agreement between CT and PET was found in 42 of 47 patients (89%). Agreement between CT and PET/CT was found in 44/47 patients (93%). All positive cases for CT were positive for PET/CT. *Thoracic*. Agreement between CT and PET was found in 39/47 patients (83%) whereas CT and PET/CT agreed in 42 of 47 patients (89%). *Abdomen-groin*. Agreement between CT and PET was found in 37 of 47 patients (78·7%). Agreement between CT and PET/CT was found in 43 of 47 patients (91%). Nodal discrepancies are shown in Table II.

For the *extranodal region*, 61·7% of patients had positive findings with CT, 57·4% with PET, whereas both PET/CT demonstrated 78% of patients with positive findings. Agreement between CT and PET was found in 25 of 47 patients (53%) whereas CT and PET/CT agreed in 76% (35 of 47 patients). In 11 patients (Table III) PET/CT was positive for extranodal findings that were indeterminate or negative for CT, 10 of whom finally had their disease stage increased. LD PET/CT and FD PET/CT showed full agreement in the extranodal region in all but one patient (Patient 3) indeterminate for FD PET/CT (HL with a doubtful adnexal mass that was not confirmed in follow/up PET/CT). It is of note, that four patients positive for PET, were negative for PET/CT (data not shown). All four cases

Table II. Nodal discrepancies.

Patient number	Diagnosis	CT	PET	PET/CTs*	Outcome/ follow-up
Cervical					
5	DLBCL	Indeterminate	Negative	Negative	Negative
14	MZL	Indeterminate	Negative	Indeterminate	Negative
47	DLBCL	Indeterminate	Positive	Positive	Positive
48	MZL	Indeterminate	negative	Negative	Negative
51	MCL	Positive	Negative	Positive	Positive
Thoracic					
11	DLBCL	Indeterminate	Negative	Negative	Negative
14	MZL	Positive	Negative	Positive	Positive
29	DLBCL	Indeterminate	Positive	Negative	Negative
30	DLBCL	Negative	Indeterminate	Negative	Negative
32	DLBCL	Positive	Indeterminate	Positive	Positive
39	HL	Indeterminate	Positive	Positive	Positive
48	MZL	Positive	Negative	Negative	Negative
50	DLBCL	Positive	Negative	Positive	Positive
51	MCL	Positive	Indeterminate	Positive	Positive
Abdomen-groin					
5	DLBCL	Negative	Positive	Positive	Positive
13	HL	Positive	Negative	Positive	Positive
14	MZL	Positive	Negative	Positive	Positive
15	MZL	Positive	Negative	Positive	Positive
23	HL	Negative	Positive	Positive	Positive
25	MZL	Positive	Negative	Positive	Positive
34	FL grade 3	Positive	Negative	Negative	Negative
37	MZL	Positive	Negative	Positive	Positive
47	DLBCL	Positive	Negative	Positive	Positive
51	MCL	Positive	Negative	Positive	Positive

DLBCL, diffuse large B cell lymphoma; MZL, marginal zone lymphoma; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; CT, computed tomography; PET, positron emission tomography.

*Both PET/CT techinques are shown in one column because the differences were insignificant.

Table III. Comparison of extranodal accuracy.

Patient number	Diagnosis	CT	PET	PET/CTs†	Extranodal finding	Outcome/follow-up
4	DLBCL	Negative	Positive	Positive	Sigmoid mass (Bx)	Negative at F/U
6	DLBCL	Negative	Positive	Positive	Parotid gland	Negative at F/U
11	DLBCL	Negative	Positive	Positive	Vertebra	Negative at F/U
18	DLBCL	Negative	Indeterminate	Positive	Base of the tongue	Negative at F/U
20	DLBCL	Negative	Indeterminate	Positive	Gastric involvement	Negative at F/U
21	FL grade 2	Negative	Positive	Positive	Parotid gland and lumbar vertebra*	Negative at F/U
26	DLBCL	Indeterminate	Positive	Positive	Sternum (not localised by PET)	Negative at F/U
28	HL	Negative	Positive	Positive	Parotid gland	Negative at F/U
34	FL grade 3	Negative	Indeterminate	Positive	Thyroid (Bx)	Negative at F/U
45	DLBCL	Negative	Positive	Positive	Thyroid	Negative at F/U
46	ACL	Indeterminate	Positive	Positive	Lung, pericardium	Negative at F/U

Bx, lymphoma involvement confirmed by biopsy; DLBCL, diffusse large B cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; ACL, anaplastic cell lymphoma; CT, computed tomography; PET, positron emission tomography.
*PET false positive for spleen hilum.
†Both PET/CT techniques are shown in one column because the differences were insignificant.

were confirmed to be negative when followed-up (Patient 13 splenic hilum, Patient 21 splenic hilum, Patient 33 gluteal uptake, Patient 44 lung).

Bone marrow biopsy positive cases. This group included 13 patients, of whom 11 suffered from NHL (three diffuse large B cell lymphoma (DLBCL), one peripheral T cell lymphoma (PTCL), one small lymphocytic lymphoma (SLL), one marginal zone lymphoma (MZL) and one mantle cell lymphoma (MCL)) and two from nodular sclerosis HL. In all cases, involvement was found in biopsy specimens obtained from one iliac crest. Findings in PET and PET/CT included focal disease in only two cases (one HL and one MZL). Eleven patients, including low- and high-grade NHL and one HL, had isolated suspicious cells, such that reactive BM changes or discrete displacement of normal marrow could not be ruled out, and all were considered negative for BM involvement by PET and PET/CT. *Bone marrow PET and PET/CT positive cases.* Both PET/CT techniques (LD and FD) were in full agreement regarding BM involvement. Three of six patients in this group suffered from nodular sclerosis HL whereas the remaining three were diagnosed with NHL (one follicular grade 2, one MZL and one DLBCL). BM biopsy confirmed PET and PET/CT findings in two of these patients (one HL and one MZL). In four cases (two HL and two NHL) neither bilateral BM biopsy nor MRI could confirm BM infiltration.

PET/CT results in the initial staging

Agreement in staging was statistically significant between the reference standard, as described above, and the three new staging algorithms by PET, LD PET/CT and FD PET/CT, with $k = 0{\cdot}54$ ($P < 0{\cdot}001$) for the algorithm using PET, $k = 0{\cdot}624$ ($P < 0{\cdot}001$) for the algorithm using LD PET-CT, and $k = 0{\cdot}628$, ($P < 0{\cdot}001$) for the one using FD PET/CT. Moreover, we found an almost perfect agreement between low-dose PET/CT and full-dose PET/CT ($k = 0{\cdot}92$, $P < 0{\cdot}001$). Both algorithms with PET/CT showed statistically significant higher stages when compared with the reference standard (McNemar test, $P = 0{\cdot}012$).

NHL. (Table IV). Discordant staging by diagnostic CT and by PET/CT was found in 10 of 31 patients (32·2%) with NHL. Disease stage was increased for all 10 patients in this group (seven DLBCL, one ACL, one FL grade 2, one FL grade 3). Upstaging was due to findings in extra nodal regions that were confirmed either by biopsy (two patients) or by follow-up (seven patients), as described above. One patient died before follow-up PET/CT could be performed (see Table IV).

HL. (Table IV). Discordant staging by diagnostic CT and by PET/CT was found in 1 of 16 patients (6·25%). This patients' disease stage was increased because PET/CT showed positive lymph nodes that were normal in size. A follow-up PET/CT showed no uptake after chemotherapy in abdominal lymph nodes. Nine patients had stage II disease by CT algorithm and this was concordant by PET/CT findings in eight patients. Six patients with advanced stage (III/IV) were detected by either CT or PET/CT.

Incidental findings

Both PET/CT modalities detected one teratoma, not seen with PET because it had no FDG uptake. A small endometrial carcinoma and one case of jugular thrombosis were only detected with FD PET/CT.

Discussion

In this study, PET/CT emerged as a powerful imaging tool for the detection of nodal involvement, extranodal disease and accurate staging of NHL and HL.

Table IV. Staging discrepancies.

Patient number	Diagnosis	AA stage (CT)	AA stage PET	AA stage PET/CT*	AA stage GOLD STANDARD
4	DLBC NHL	II	IV	IV	IV (biopsy: sigmoid involvement)
6	DLBC NHL	III	IV	IV	IV (F/U parotid gland involved)
11	DLBC NHL	III	IV	IV	IV (F/U vertebra involved)
18	DLBC NHL	II	IV	IV	Died during first course of chemotherapy
20	DLBC NHL	III	IV	IV	IV (F/U stomach involved)
21	FL grade 2 NHL	III	IV	IV	IV (F/U parotid gland and vertebra involved)
23	NS HL	II	III	III	III (F/U infradiaphragmatic lymh nodes negative after therapy)
26	DLBC NHL	II	II	IV	IV (F/U sternum involved)
34	FL grade 3 NHL	III	I	IV	IV (biopsy: thyroid involved)
45	DLBC NHL	II	II	IV	IV (sternum and thyroid involvement)
46	ACL	II	IV	IV	IV (lung and pericardium involved)

AA, Ann Arbor; LD, low dose non-enhanced; FD, full dose enhanced; DLBCL, diffusse large B cell lymphoma; FL, follicular lymphoma; NS, nodular sclerosis; HL, Hodgkin lymphoma; ACL, anaplastic cell lymphoma; CT, computed tomography; PET, positron emission tomography.
* Both PET/CT techniques are shown in one column because the differences were insignificant.

PET/CT accuracy for lymph node involvement

Accuracy for lymph node infiltration of NHL and HL, analysed on a per-patient basis, was superior for PET/CT compared with contrast-enhanced CT and PET alone. Combined PET/CT markedly increased accuracy for the detection of infradiaphragmatic involvement by lymphoma. These findings agree with those of Beyer *et al* (2000) and Buchmann *et al* (2001), who reported that FDG PET was insufficient for the precise anatomical localisation of foci of abnormal uptake in the abdomen.

Extranodal malignant lymphoma detection

Increased uptake of FDG in liver, skeleton (uni or multifocal) and other extranodal sites (thyroid, bowel, parotid gland.) has been reported while in CT the involved organs showed minimal to moderate enlargement and patients had no subjective complaints (Sam *et al*, 2002). PET/CT is a particularly promising method for evaluating extranodal sites since allows for precise localisation of anatomical structures showing increased FDG uptake (Schaefer *et al*, 2004). About 78% of patients in our study had positive findings for extranodal regions for PET/CT and 10 of 31 NHL patients (see Table IV) had their disease stage increased due to extranodal disease detected by PET/CT that was not detected by CT (Fig 1).

PET-CT detection of lymphomatous bone marrow

Positive BM biopsy forms a criterion for stage IV disease leading to therapeutic and prognostic consequences. PET efficacy in evaluating BM involvement led to 80% sensitivity and 100% specificity upgrading stage in 10% of patients in some studies (Moog *et al*, 1998a). In our study PET and BM biopsy had concordant positive results in two cases (2·5%) and concordant negative results in 30 patients (63%). Thus, combined PET/CT did not increase sensitivity in detecting BM involvement by malignant lymphoma.

Histology and FDG uptake

In a retrospective study of 172 patients (Elstrom *et al*, 2003), FDG accurately detected disease in DLBCL patients, MCL, FL and HL, but it was less reliable in detecting MZL (50% of cases detected) and SLL. It is of interest that in our series, none of the six patients with MZL histology was positive for PET activity neither in spleen nor in peripheral lymph nodes. By contrast, PET was 100% reliable for DLBCL and HL. These results agree with the review by Burton *et al* (2004), who found PET/CT of great value in HL and histologically aggressive NHL patients. The small number of patients with other subtypes (FL, SLL, ATCL, PTCL, MCL and Burkitt's NHL) did not allow accurate interpretation of these results.

PET/CT for initial staging accuracy

Before PET/CT was available, most studies evaluating the role of PET in the diagnostic staging of lymphoma were retrospective. Prospective studies (Bangerter *et al*, 1998; Weihrauch *et al*, 2002) showed an overall upstaging of patients with PET staging algorithms. Schöder *et al* (2001) reported more than 60% change in management of patients compared to 10–34% published by other authors (Bangerter *et al*, 1998; Moog *et al*, 1998b; Shah *et al*, 2000). To our knowledge, there are no prospective studies comparing PET/CT and CT for initial staging in lymphoma patients. In our study PET/CT significantly increased disease stage when compared with CT (see Table IV). This was particularly evident in NHL, due to extranodal disease not detected by CT or PET (Fig 2).

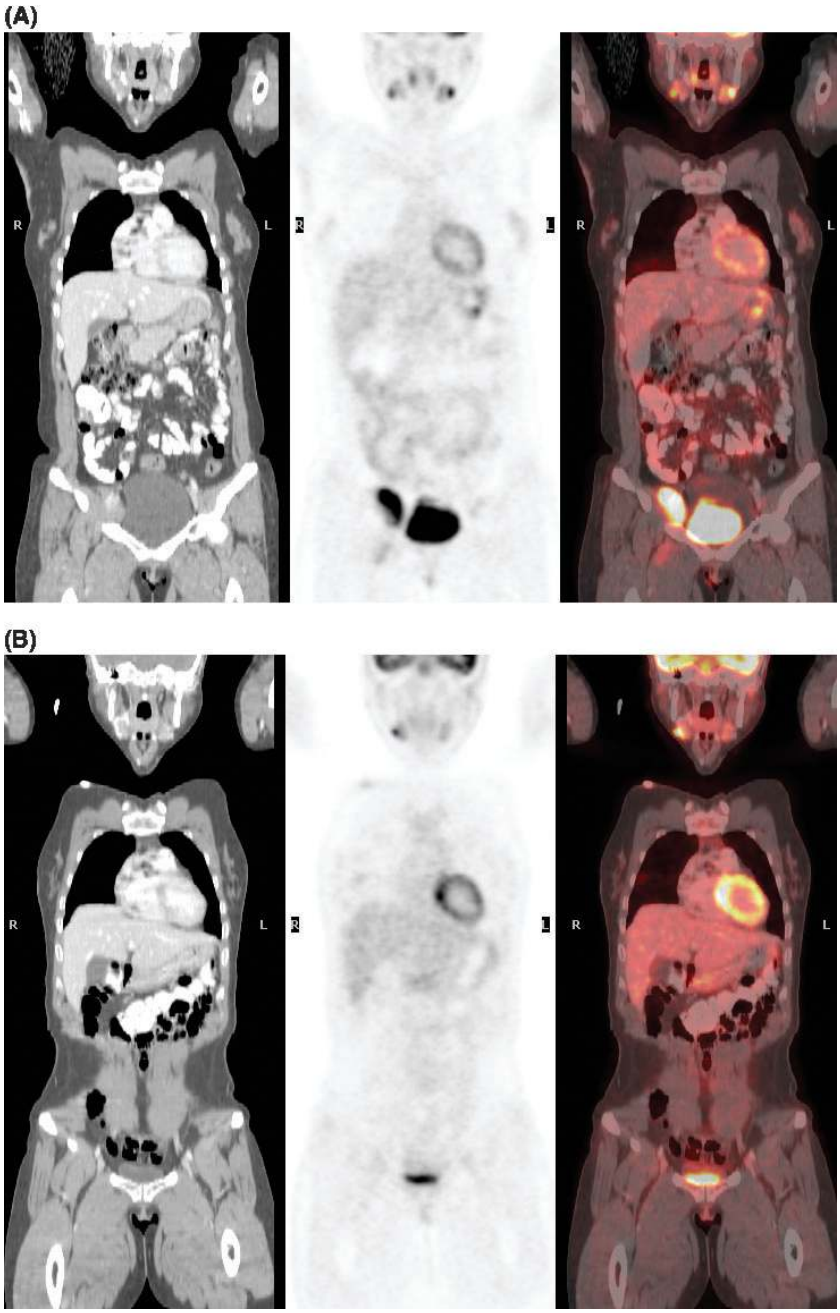

Fig 1. Thirty-two-year-old female. (A) Pre-treatment Coronal computed tomography (CT) images show enlarged right inguinal lymph nodes. Positron emission tomography (PET) depicts increased FDG uptake in right inguinal region and a faint curvilinear foci in the left upper quadrant. PET/CT revealed gastric involvement by DLBCL. (B) After first-line ProMACE-Rituxan chemotherapy (3 cycles) the patient achieved complete remission, showing no abnormal FDG uptake foci.

Subsequent PET/CT restaging after chemotherapy and/or biopsy of suspected extranodal lesions demonstrated PET/CT accuracy (Tables III and IV).

An almost excellent agreement between low dose non-enhanced PET-CT and full dose enhanced CT in nodal detection and staging ($k = 0{\cdot}92$, $P < 0{\cdot}001$) derived from our study concurred with the previously published results (Schaefer *et al*, 2004). Therefore a reasonable approach would be to omit the standard full dose enhanced CT and perform PET/CT as the sole baseline study, which would significantly reduce radiation exposure at diagnosis. This initial PET/CT would provide an accurate baseline study to assign initial stage and also for comparison at restaging. Whether this PET/CT should be performed with low dose non-enhanced CT or full dose enhanced CT needs further investigation.

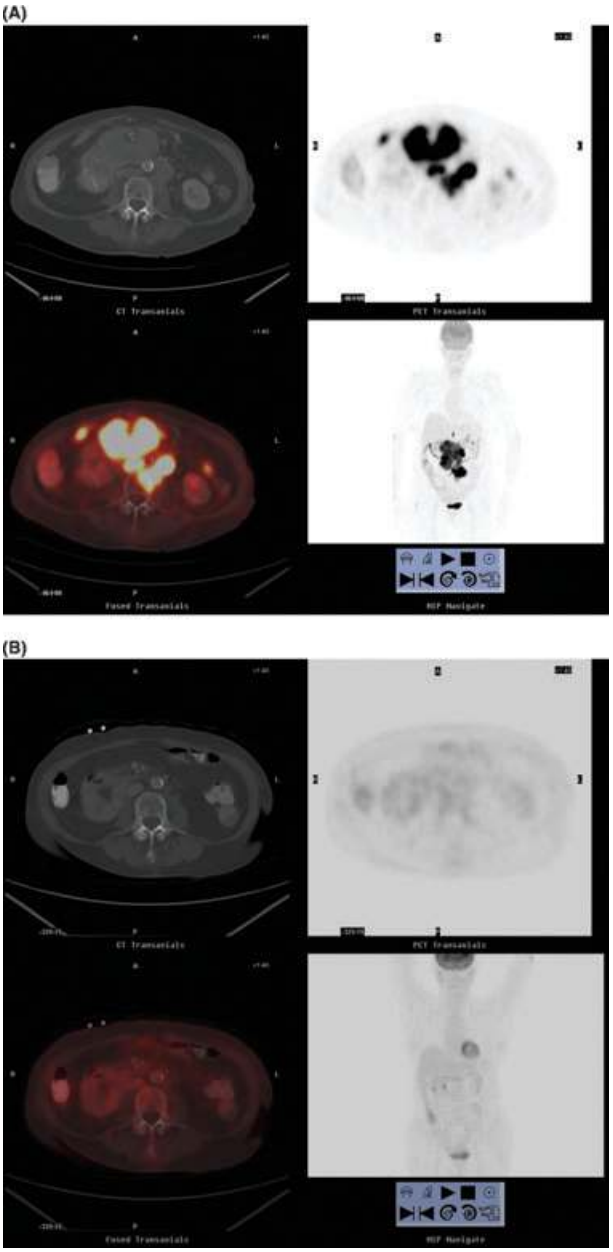

Fig 2. Seventy-five-year-old female with lumbar vertebra involvement by diffuse large B cell lymphoma not detected by computed tomography (CT). (A) Pre-treatment. A CT failed to depict L5 involvement, showing only infradiaphragmatic para-aortic and mesenteric enlarged lymph nodes. Positron emission tomography (PET) shows increased uptake by retroperitoneal lymph nodes (max. SUV = 18·3). PET/CT clearly shows increased FDG uptake by L5 vertebra. PET fails to precisely localise increased FDG uptake. (B) After 3 cycles of ProMACE chemotherapy, CT shows no abnormal sites and PET and PET/CT show no increased uptake at corresponding sites.

PET/CT and treatment approach

In our study, the results obtained with PET/CT induced modifications in the treatment of seven of 11 patients that had their disease stage increased (six NHL and one HL). Globally different treatment was suggested for seven of 47 patients (14·8%). It is of interest that a change in therapy does not necessarily improve survival (Burton *et al*, 2004), as the better choice of therapy may be counterbalanced by poorer prognosis due to an advance in the staging of these patients.

Study limitations

A limitation of the current study is the patient population, composed of different NHL and HL subtypes and small numbers of patients for some NHL subgroups. Another shortcoming, inherent to other published studies (Raanani *et al*, 2006), is the verification of malignant and non-malignant lesions due to the fact that biopsy of affected sites is not always indicated in lymphoma patients.

Conclusions and future directions

In summary, PET/CT is an accurate imaging diagnostic tool that provides, in a single session, a complete body survey of the affected areas in a disease with an unpredictable clinical course, such as lymphoma. In our study, the κ statistic showed excellent agreement between LD PET/CT and FD PET/CT for lymph node detection and organ involvement. Compared with CT and PET, PET/CT improves accuracy in the detection of infradiaphragmatic nodal disease, extranodal lymphoma, and significantly improves initial staging of patients with lymphoma. PET/CT is of great value on aggressive NHL and HL because it provides a baseline to evaluate treatment response.

Acknowledgements

Authors would like to acknowledge Dr Jose Martinez and Dr Ana de la Rua for their help in reviewing the manuscript. This work was supported by FIS (Health Investigation Fund) Grant-03/0149.

References

Alessio, A.M., Kinahan, P.E., Cheng, P.M., Vesselle, H. & Karp, J.S. (2004) PET/CT scanner instrumentation, challenges and solutions. *Radiologic Clinics of North America*, **42,** 1017–1032.

Bangerter, M., Moog, F., Buchmann, I., Kotzerke, J., Griesshammer, M., Hafner, M., Elsner, K., Frickhofen, N., Reske, S.N. & Bergmann, L. (1998) Whole-body 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography for accurate staging of Hodgkin's disease. *Annals of Oncology*, **9,** 1117–1122.

Bar-Shalom, R., Mor, M., Yefremov, N. & Goldsmith, S.J. (2001) The value of Ga-67 scintigraphy and F-18 fluorodeoxyglucose positron emission tomography in staging and monitoring the response of lymphoma to treatment. *Seminars in Nuclear Medicine*, **XXXI,** 177–190.

Bar-Shalom, R., Yefremov, N., Haim, N., Dann, E.J., Epelbaum, R., Keidar, Z., Gaitini, D., Frenkel, A. & Israel, O. (2003) Camera-based FDG PET and ^{67}Ga SPECT in evaluation of lymphoma: comparative study. *Radiology*, **227,** 353–360.

Beyer, T., Townsend, D.W., Brun, T., Kinahan, P.E., Charron, M., Roddy, R., Jerin, J., Young, J., Byars, L. & Nutt, R. (2000) A combined PET/CT scanner for clinical oncology. *Journal of Nuclear Medicine*, **41,** 1369–1379.

Buchmann, I. & Reske, S.N. (2001) Novel imaging techniques in NHL: clinical results with PET imaging. *Annals of Hematology*, **80,** B54–B57.

Buchmann, I., Reinhardt, M., Elsner, K., Bunjes, D., Altehoefer, C., Finke, J., Moser, E., Glatting, G., Kotzerke, J., Guhlman, C.A., Schirrmeister, H. & Reske, S.N. (2001) 2-(fluorine-18) fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. *Cancer*, **91,** 889–899.

Burton, C., Ell, P. & Lynch, D. (2004) The role of PET imaging in lymphoma. *British Journal of Haematology*, **126,** 772–784.

Carbone, P., Kaplan, H.S., Muschoff, K., Smithers, D.W. & Tubiana, M. (1971) Report of the committee on Hodgkin's disease staging classification. *Cancer Research*, **31,** 1860.

Elstrom, R., Guang, L., Baker, G., Nakhoda, K., Vergilio, J.A., Zhuang, H., Pitsilos, S., Bagg, A., Downs, L., Mehrotra, A., Kim, S., Alavi, A. & Schuster, S.J. (2003) Utility of FDG-PET scanning in lymphoma by WHO classification. *Blood*, **101,** 3875–3876.

Evans, L.S. & Hancock, B.W. (2003) Non-Hodgkin lymphoma. *Lancet*, **362,** 139–146.

Friedberg, J.W. & Chengazi, V. (2003) PET scans in the staging of lymphoma: current status. *The Oncologist*, **8,** 438–447.

Gdeedo, A., Van Schil, P., Corthouts, B., Van Mieghem, F., Van Meerbeck, J. & Van Marck, E. (1997) Prospective evaluation of computed tomography and mediastinoscopy in mediastinal lymh node staging. *European Respiratory Journal*, **10,** 1547–1551.

Ha, C.S., Choe, J.G., Kong, J.S., Allen, P.K., Oh, Y.K., Cox, J.D. & Kim, E.E. (2000) Agreement rates among single photon emission computed tomography using gallium-67, computed axial tomography and lymphangiography for Hodgkin disease and correlation of image findings with clinical outcome. *Cancer*, **89,** 1371–1379.

Hany, T.F., Steinert, H.C., Goerres, G.W., Buck, A. & Von Schulthess, G.K. (2002) PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. *Radiology*, **225,** 575–581.

Harris, N.L., Jaffe, E.S., Diebold, J., Flandrin, G., Muller-Hermelink, H.K., Vardiman, J., Lister, T.A. & Bloomfield, C.D. (1999) World Health Organization of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *Journal of Clinical Oncology*, **17,** 3835–3849.

Hasenclever, D. & Diehl, V. (1998) A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on advanced Hodgkin's disease. *New England Journal of Medicine*, **339,** 1506–1514.

Hoh, C.K., Glaspy, J., Rosen, P., Dahlbom, M., Shay, J.L., Kunkel, L., Hawkin, R.A., Maddahi, J. & Phelps, M.E. (1997) Whole-body FDG-PET imaging for staging of Hodgkin's disease and lymphoma. *Journal of Nuclear Medicine*, **38,** 343–348.

Hutchings, M., Mikhaeel, N.G., Fields, P.A., Nunan, T. & Timothy, A.R. (2005) Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. *Annals of Oncology*, **16,** 1160–1168.

Jerusalem, G., Hustinx, R., Beguin, Y. & Fillet, G. (2005) Positron emission tomography imaging for lymphoma. *Current Opinion in Oncology*, **17,** 441–445.

Juweid, M.E. & Cheson, B.D. (2006) Current concepts: positron-emission tomography and assessment of cancer therapy. *New England Journal of Medicine*, **354,** 496–507.

Kostakoglu, L., Leonard, J.P., Kuji, I., Coleman, M., Vallabhajosula, S. & Goldsmith, S.J. (2002) Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. *Cancer*, **94,** 879–888.

Lister, R. & Crowther, D. (1990) Staging for Hodgkin's disease. *Seminars of Oncology*, **17,** 696.

Moog, F., Bangerter, M., Diederichs, C.G., Guhlmann, A., Kotzerke, J., Merkle, E., Kolokythas, O., Herrmann, F. & Reske, S.N. (1997) Lymphoma: role of 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) PET in nodal staging. *Radiology*, **203,** 795–800.

Moog, F., Bangerter, M., Kotzerke, J., Guhlmann, A., Frickhofen, N. & Reske, S.N. (1998a) 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. *Journal of Clinical Oncology*, **16,** 603–609.

Moog, F., Bangerter, M., Diederichs, C.G., Guhlmann, A., Merkle, E., Frickhofen, N. & Reske, S.N. (1998b) Extranodal malignant lymphoma: detection with FDG-PET versus CT. *Radiology*, **206,** 475–481.

Paul, R. (1987) Comparison of F-18-2-FDG and gallium-67 citrate imaging for detection of lymphoma. *Journal of Nuclear Medicine*, **28,** 288–292.

Phelps, M.E. (2000) PET: the merging biology and imaging into molecular imaging. *Journal of Nuclear Medicine*, **41,** 661–681.

Raanani, P., Shasha, Y., Perry, C., Metser, U., Naparstek, E., Apter, S., Nagler, A., Polliack, A., Ben-Bassat, I. & Even-Sapir, E. (2006) Is CT scan still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era? *Annals Oncology*, **17,** 117–122.

Re, D., Thomas, R.K., Behringer, K. & Diehl, V. (2005) From Hodgkin disease to Hodgkin lymphoma: biologic insights and therapeutic potential. *Blood*, **105,** 4553–4560.

Rini, J.N., Manalili, E.Y., Hoffman, M.A., Karayalcin, G., Mehrotra, B., Tomas, M.B. & Palestro, C.J. (2002) F-18 FDG versus Ga-67 for detecting splenic involvement in Hodgkin's disease. *Clinical Nuclear Medicine*, **27,** 572–577.

Römer, W. & Schwaiger, M. (1998) Positron emission tomography in diagnosis and therapy monitoring of patients with lymphoma. *Clinical Positron Imaging*, **1,** 101–110.

Sam, J.W., Levine, M.S., Farner, M.C., Schuster, S.J. & Alavi, A. (2002) Detection of small bowel involvement by mantle cell lymphoma on F-18 FDG positron emission tomography. *Clinical Nuclear Medicine*, **27,** 330–333.

Schaefer, N.G., Hany, T.F., Taverna, C., Seifert, B., Stumpe, K., von Schulthess, G.K. & Goerres, G.W. (2004) Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging-Do we need contrast-enhanced CT? *Radiology*, **232,** 823–829.

Segall, G.M. (2001) FDG PET imaging in patients with lymphoma: a clinical perspective. *Journal of Nuclear Medicine*, **42,** 609–610.

Shah, N., Hoskin, P., McMillan, A., Gibson, P., Lowe, J. & Wong, W.L. (2000) The impact of positron emission tomography imaging on the management of lymphomas. *The British Journal of Radiology*, **73,** 482–487.

Solal-Celigny, P., Roy, P., Comolmbat, P., White, J., Armitage, J.O., Arranz-Saez, R., Au, W.Y., Bellei, M., Brice, P., Caballero, D., Coiffier, B., Conde-Garcia, E., Doyen, C., Federico, M., Fisher, R.I.,

Garcia-Conde, J.F., Guglielmi, C., Hagenbeek, A., Haioun, C., LeBlanc, M., Lister, A.T., Lopez-Guillermo, A., McLaugghlin, P., Milpied, N., Morel, P., Mounier, N., Proctor, S.J., Zinzani, P.L., Zucca, E. & Montserrat, E. (2004) Follicular lymphoma international prognostic index. *Blood*, **104,** 1258–1265.

Steinert, H.C. (2004) PET/CT in lymphoma patients. *Radiologe*, **44,** 1060–1067.

Tatsumi, M., Kitayama, H., Sugahara, H., Tokita, N., Nakamura, H., Kanakura, Y. & Nishimura, T. (2001) Whole-body hybrid PET with ^{18}F-FDG in the staging of non-Hodgkin's lymphoma. *Journal of Nuclear Medicine*, **42,** 601–608.

The International Non-Hodgkin's lymphoma Prognostic factors Project. (1993) A predictive model for aggressive non-Hodgkin's lymphoma. *New England Journal of Medicine*, **329,** 987–994.

Townsend, D.W. (2001) A combined PET/CT scanner: the choices. *Journal of Nuclear Medicine*, **42,** 533–534.

Townsend, D.W. & Beyer, T. (2002) A combined PET/CT scanner: the path to true image fusion. *British Journal of Radiology*, **75,** S24–S30.

Von Schultess, G.K., Steinert, H.C. & Hany, T.F. (2006) Integrated PET/CT: current applications and future directions. *Radiology*, **238,** 405–422

Weihrauch, M.R., Re, D., Bischoff, S., Dietlein, M., Scheidhauer, K., Krug, B., Textoris, F., Ansén, S., Franklin, J., Bohlen, H., Wolf, J., Schicha, H., Diehl, V. & Tesch, H. (2002) Whole-body positron emission tomography using 18F-fluorodeoxyglucose for initial staging of patients with Hodgkin's disease. *Annals of Hematology*, **81,** 20–25.