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Are ^{18}fluorodeoxyglucose positron emission tomography and magnetic resonance imaging useful in the prediction of relapse in lymphoma residual masses?

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Abstract

Treatment of both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) frequently results in a residual mass visible radiologically. Such patients may receive radiotherapy unnecessarily because the residual mass may represent benign fibrotic tissue rather than residual active lymphoma. Radiotherapy has been shown to have significant short and more worrying long-term toxicity. Refining the criteria for its use would be a major advance. A number of clinical investigations have been evaluated to more accurately determine the nature of such lesions, including erythrocyte sedimentation rate (ESR), magnetic resonance imaging (MRI) and high-dose gallium-67 scanning (HDGS) but none has proven utility. ^{18}[F]-fluorodeoxyglucose positron emission tomography (FDG-PET) is an imaging technique that has been shown to be useful in distinguishing fibrosis from residual active disease in solid tumours. The aim of this study was to compare FDG PET and MRI in the assessment of residual masses following treatment for lymphoma. Patients with NHL/HD who had a residual mass following chemotherapy were eligible for this study. Patients had a combination of MRI and/or PET. All scans were completed within 5 months of the end of treatment. Patients were followed-up for relapse. 56 patients had an MRI scan, 24 had a PET scan and 22 patients had both investigations. Overall sensitivity and specificity, respectively, were for MRI 45% and 74%, PET 50% and 69%, and PET/MRI concurring 50% and 67%. There was a trend for improved relapse-free survival (RFS) with a negative result of both MRI and PET, but this was not statistically significant. The predictive value for both tests failed to reach statistical significance. Subgroup analysis suggests that PET may be better at predicting relapse in patients with NHL, especially those with masses above the diaphragm. There is no convincing evidence that either MRI or PET or the combination can reliably predict relapse within residual masses after treatment for lymphoma. A negative PET scan however appears to be more informative than a positive result and may well aid clinical decision making. There are a number of factors that may produce false-positive results, including post-treatment inflammatory changes, the sensitivity of the test in the setting of minimal residual disease and the heterogeneity of the histological subtypes studied. A negative PET (or MRI) result in lymphoma residual masses following therapy may negate the necessity for further therapy such as chemotherapy or radiotherapy and their concomitant toxicities.

Keywords: Hodgkin's disease; Non-Hodgkin's lymphoma; Positron emission tomography; Fluorodeoxy-F-18; Magnetic resonance imaging; Residual disease

1. Introduction

Treatment of both Hodgkin's and non-Hodgkin's lymphoma (NHL) frequently results in residual masses detected radiologically [1]. A proportion of these patients will have been cured as the mass contains only benign tissue. The precise aetiology of these residual masses is likely to be multifactorial, with proposed mechanisms including reactions stimulated by therapy [2], thymic involvement of Hodgkin's disease (HD) [3], or remnants of tumour related fibrotic stroma [4]. Others however, will have remaining active disease within the residual mass [1]. The proportion of residual masses that represent active lymphoma varies between series. In their series of 65 patients with HD and post therapy residual masses, Jochelson and colleagues [5] reported a relapse rate of 19–20%. Radford and colleagues [6]

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reported a similar relapse rate of 19%. Surbonne and colleagues [1] investigated the pathology of residual masses in aggressive NHL. They found that the pathological and clinical relapse rate in their series of 29 residual masses was 10%.

Despite the clear benefit of radiotherapy in limited stage lymphoma, there is conflicting evidence concerning its use in advanced disease. There is data on the use of radiotherapy in patients with initial bulky disease, but there is scarce information in the setting of a residual mass *per se*. In a meta-analysis of adjuvant radiotherapy in advanced HD, Loeffler and associates [7] reported the results of chemotherapy versus chemotherapy and adjuvant radiotherapy in 918 patients. They found an 11% benefit in continuous complete remission in patients receiving radiotherapy. However, this benefit was absent in patients with stage IV disease, and there was no additional benefit in patients with initial bulky disease. They also found that radiotherapy gave no benefit in overall survival. Aviles and colleagues [8] looked at the pattern of relapse in patients with stage IV large cell NHL after treatment with standard chemotherapy cyclophosphamide, epirubicin, vincristine, prednisalone and bleomycin (CEOP-BLEO) with or without subsequent radiotherapy. All patients had an initial bulk of 10 cm or more. The relapse rate in the radiotherapy arm was 28% compared with 64% in the non-radiotherapy arm. However, only 2 of the patients relapsing in the radiotherapy arm (4.6%) relapsed in the old site alone and so it is unclear whether radiotherapy to a residual mass alone would alter outcome.

A proportion of patients with residual abnormalities who receive radiotherapy probably do so unnecessarily, and are, therefore, also being exposed to avoidable toxicity. This is an especially important issue since many of these patients are both young and curable, thus having a normal life expectancy. A study by Gustavsson and coworkers [9] showed that out of 26 patients aged 21–25 years old treated 10–20 years previously with mantle radiotherapy alone, 4 patients (15%) had serious cardiac complications including 3 with ischaemic heart disease and 1 with constrictive pericarditis. Other sequelae of radiotherapy include hypothyroidism and pulmonary complications (such as reduced diffusing capacity and lung volume) [10], as well as an increase in haematological malignancy and solid tumours. In a study by van Leeuwan and associates [11] there was a greater than 40-fold increased risk of breast cancer after 15 years following radiotherapy in women aged less than 20 years at the time of radiotherapy.

A number of different techniques have been used to try to distinguish active from inactive in the context of residual lymphoma masses. High-dose gallium-67 scintigraphy (HDGS), erythrocyte sedimentation rate (ESR), and magnetic resonance imaging (MRI) have all been investigated as predictors of tumour activity, relapse and overall survival in patients with or without residual abnormalities. The study by Hagemeister and coworkers [12] of 240 gallium scans in 165 patients demonstrated that 95% of unsuspected relapses were missed by the scan. Post-treatment ESR has been shown to be an independent predictor of early relapse in HD after radiotherapy [13].

In a previous study of magnetic resonance of residual masses at the Royal Marsden Hospital [14], MRI had a sensitivity of only 38%, but a specificity of 90% for predicting relapse. The positive and negative predictive values were 71% and 70%, respectively.

Positron emission tomography (PET) is a functional imaging technique using biologically active compounds labelled with positron emitters, such as ^{18}[F]-fluorodeoxyglucose (^{18}FDG). The use of ^{18}FDG for *in vivo* cancer imaging is based on the observation of enhanced glycolysis in tumour cells first described by Warburg in the early part of this century [15]. There appears to be upregulation of glucose transporters, of which GLUT1 and GLUT3 have been shown to be overexpressed in several human cancer types. An increase in the activity of several enzymes of the glycolytic pathway (including hexokinase, phosphofructokinase and pyruvate dehydrogenase) has also been demonstrated. Following conversion by hexokinase, the phosphorylated form of ^{18}FDG does not react with glucose-6-isomerase, the second enzyme in the glycolytic pathway. Since dephosphorylation by glucose-6-phosphatase is very slow, ^{18}FDG-6-phosphate is essentially trapped within the cell. Thus, the intracellular ^{18}FDG accumulation is a reflection of glucose uptake and glycolytic activity of the cell.

This technique has been applied to several aspects of oncological imaging, including differential diagnosis, initial staging, demonstration of disease recurrence, follow-up therapy and prognostic information [16]. ^{18}FDG PET has been found to be a technique with high sensitivity for the detection of active tumour.

There have been limited published data on the application of ^{18}FDG PET in the evaluation of residual masses following treatment for lymphoma. This study was designed to determine the utility of ^{18}FDG PET in the evaluation of residual masses following treatment for lymphoma, and to compare this with the results from MRI. In addition, we have extended the series of patients having MRI in this setting from 34 to 56.

2. Patients and methods

2.1. Patient selection

Patients were studied in whom there were residual masses on computed tomography (CT) scan after treat-

ment for HD or intermediate- to high-grade NHL. Masses that showed no response to treatment or that had not remained stable in size over two courses of chemotherapy (after an initial response) were excluded. Patients were recruited prospectively between April 1990 and March 1991 apart from 2 who completed treatment in 1988, who were analysed retrospectively. The initial series was extended by 30 patients fulfilling the same criteria. Patients were recruited from June 1993 to February 1996. All initial investigations (the first MRI and PET scans) were completed within 5 months of completing therapy. All patients gave fully informed consent and the study was approved by the local ethics committee.

2.2. MRI

All images were obtained through the area of interest in the axial plane in a 1.5 Tesla system (Siemens Medical Systems, Erlanen, Germany). Double-echo T2-weighted spin-echo (repetition time (TR), 2000–2500 msec; echo time (TE), 25–30/70–90 msec) and T1-weighted (TR, 500–700 msec; TE, 17–20 msec) sequences were used. Slice thickness was 8–10 mm contiguous or with a 2 mm gap. Coronal or sagittal scans were added if indicated to clarify anatomy.

Electrocardiogram (ECG) gating was used in all cases. The images were reviewed by a single radiologist experienced in MRI, without knowledge of the patient's treatment or other investigations. A pattern recognition technique was used [17]. The residual mass was assessed for overall homogeneity or heterogeneity. The overall signal intensity of the mass on T1- and T2-weighted images was documented as low or high. Low signal intensity on T1-weighted images was defined as signal intensity less than or equal to muscle and on T2-weighted images as less than or equal to fat; high signal intensity was defined as signal intensity greater than that of muscle on T1-weighted and greater than that of fat on T2-weighted images. If an area of the mass had high signal intensity comparable with that of cerebrospinal fluid on T2-weighted images, it was presumed to represent fluid. The mass was classified as inactive if the overall signal intensity of the mass on T2-weighted images was low heterogeneous or homogeneous. If the overall signal intensity of the mass on T2-weighted images was high heterogeneous or homogeneous the mass was classified as active disease. All masses were classified as either active or inactive, and no patient was withdrawn on the grounds of technical or interpretative difficulty.

2.3. ^{18}FDG-PET

List mode data were acquired on the multiwire proportional PET (MUP-PET) positron camera. This consists of two large area multiwire proportional chambers mounted on a rotating gantry [18]. The detectors have a field of view of 30 cm axially and up to 60 cm transaxially. These data were backprojected into a 64^3 matrix, with cubic voxel dimensions of length 0.6 cm. Backprojected images were attenuation- and scatter-corrected and deconvolved with an experimentally determined point spread function.

Patients were fasted for at least 4 h prior to the scan. An administration of 50–150 MBq ^{18}FDG was given 1 h prior to the scan. Scans were acquired for 30–45 min, enabling 1.5 million coincidence events to be collected.

Where there was uptake corresponding to the abnormality on CT, region of interest (ROI) analysis was carried out on a volume of $4 \times 4 \times 1$ voxels (0.216 cm^3) surrounding the area of maximum intensity on each scan. Background values were determined from contralateral ROIs. Corrections were also made for any remaining background.

Because of the subjective nature of the assessment, interobserver variability was reduced by consensus review by 3 personnel, including a radiologist and 2 nuclear medicine physicists experienced in PET. A positive scan was taken as an increased FDG uptake within the area of the abnormality on the CT scan above the background value. The scans were read in conjunction with the CT scans, but personnel were blinded to all other clinical and radiological data.

2.4. Follow-up

Patients were seen at regular intervals and monitored for signs and symptoms of relapse. Relapse was defined using standard World Health Organisation (WHO) clinical and radiological criteria [19]. The elapsed time from finishing treatment to relapse was recorded and patients who did not relapse have been followed up to the time of writing at regular intervals.

2.5. Statistical analysis

Categorical data were examined using the Chi-squared test, with Fisher's exact test used where expected cell counts were less than 5. Predictivity values were calculated according to the standard methods of Altman [20]. Survival analysis was performed using the product limit method of Kaplan and Meier and differences between survival curves calculated using the log rank test. Time to relapse was calculated from the date of the scan (PET or MRI) in all patients. Patients who did not relapse were censored at the date of the last follow-up. Standard definitions were used for sensitivity, specifictiy, positive predictive value (PPV) and negative predictive value (NPV). A 'true positive' result was taken as a positively detected relapse within the residual mass only.

3. Results

61 patients were recruited for this study. 3 patients were excluded from the analysis for the following reasons: 1 patient erroneously underwent a PET scan while still on treatment and 2 patients had further treatment prior to relapse. 56 patients had an MRI scan, 24 patients had a PET scan and 22 patients had both investigations (Fig. 1). Patient data are listed in Table 1.

The median follow-up time (or time to relapse or death) in the original group of patients was 34 months (range: 1–94 months). In the present study the median follow-up (or time to relapse or death) was 29 months (range: 1–64 months). During the period of the study 27 patients relapsed. 24 patients relapsed within the site of the residual mass, and 3 patients relapsed outside. In the patients that relapsed, the median time to relapse was 3 months (range: 1–34). The median time of follow-up in the non-relapsers was 63.5 months (range: 26–94).

The relapse-free survival curves are shown for PET and MRI in Fig. 2. There was no significant difference in the probability of remaining relapse free with a positive or negative result of either test. However, there was a trend for improved relapse-free survival with a negative result of either test.

The results of the post-treatment tests are listed in Table 2. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) data are shown in Table 3.

PET and MRI had a similar accuracy overall (Table 3). The sensitivity and specificity were poor, being 50% and 69% with PET, and 45% and 74% with MRI respectively. The combination of PET and MR1 with concurring results had a sensitivity of 50% and a specificity of 67%. PET in NHL patients only, had a sensitivity of 80% and a specificity of 71%. The PPV and NPV were 67% and 83%, respectively. MRI in the same patients gave a much reduced sensitivity of 44%, but a

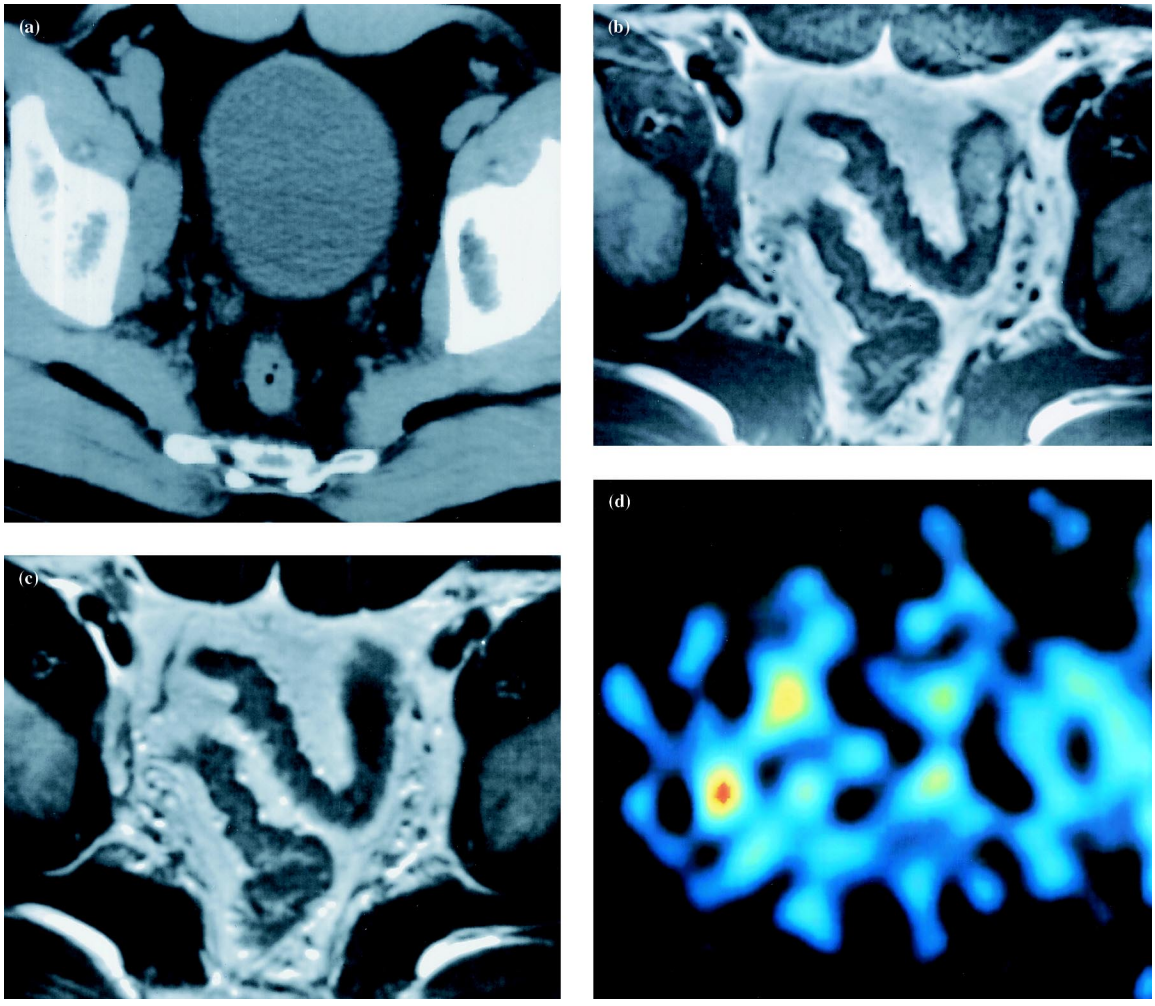

Fig. 1. Multi-modality imaging in a non-Hodgkin's lymphoma (NHL). (a) A computed tomography scan following chemotherapy shows a residual soft tissue mass of nodal lymphoma on the right pelvic wall. The magnetic resonance imaging (MRI) scan shows that the the mass has (b) a low signal intensity on T1-weighting and (c) a high signal intensity on T2-weighting. (d) ^{18}FDG-positron emission tomography (PET) scan shows high uptake of ^{18}FDG within the original mass. The patient relapsed in the abdomen 4 weeks after the MRI and PET studies.

Table 1
Patient data

No. of cases (*n*)	58
Mean age (range)	38 (17–67) years
Sex	(*n*) (%)
Male	26 (45)
Female	32 (55)
Histology	
Hodgkin's disease	33 (57)
Non-Hodgkin's lymphoma (WF D-H)	25 (43)
Stage	
I	4 (7)
II	25 (43)
III	13 (22)
IV	16 (28)
B symptoms	
Present	24 (41)
Absent	34 (59)
Treatment	
Chemotherapy	47 (81)
Chemotherapy and radiotherapy	9 (16)
Radiotherapy	2 (3)
Site of mass	
Above diaphragm	41 (71)
Below diaphragm	17 (29)
Mean size (range)	3.025 (0.5–7.0) cm
Site of relapse[a]	
Within residual mass	23
Outside residual mass	4
Total no. of relapses	27

[a] 27 sites of relapse only.

Table 2
Results of the MRI and PET scans

	Scan result (*n*)	Relapses within RM	Relapse outside RM	No relapse	*P*
PET in all patients	+ (9)	4	0	5	0.64
	− (15)	4	2	9	
MRI in all patients	+ (19)	10	1	8	0.14
	− (37)	12	3	22	
PET in NHL	+ (6)	4	0	2	0.24
	− (6)	1	1	4	
MRI in NHL	+ (8)	4	0	4	0.91
	− (16)	5	2	9	(1 tail)
PET in HD	+ (3)	0	0	3	0.76
	− (9)	3	1	5	
MRI in HD	+ (11)	6	1	4	0.44
	− (21)	7	1	13	

The predictive value for either test failed to reach statistical significance.

RM, residual mass; MRI, magnetic resonance imaging; PET; position emission tomography; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease.

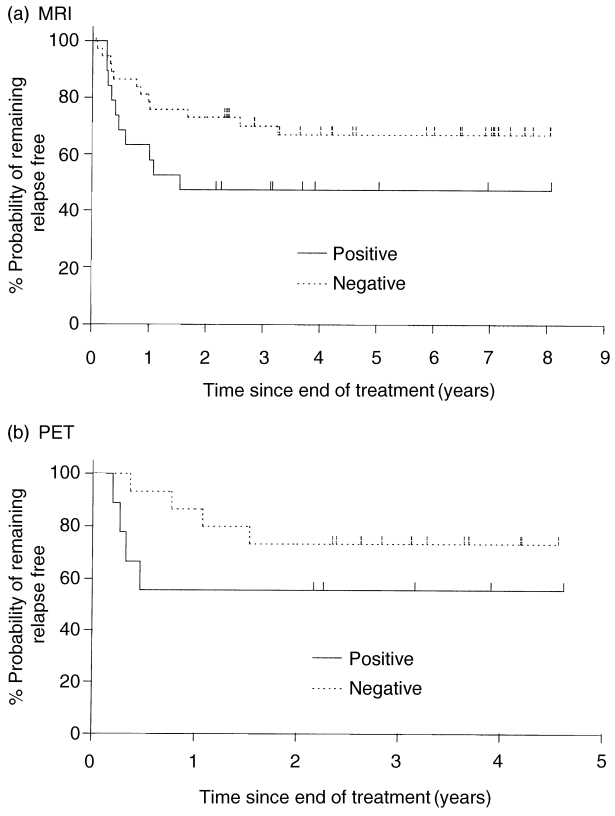

Fig. 2. The relapse-free survival curves are shown for positron emission tomography (PET) and magnetic resonance imaging (MRI). There was no significant difference in the probability of remaining relapse free with a positive or negative result of either test ($P = 0.24$ for PET, $P = 0.11$ for MRI).

Table 3
Accuracy data for PET and MRI scans

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PET all patients	50	69	44	73
MRI all patients	45	74	53	68
Concurring result for PET and MRI, all patients	50	67	33	80
PET in NHL	80	71	67	83
MRI in NHL	44	73	50	69
PET in HD	0	67	0	67
MRI in HD	46	74	55	67
PET < 6 months	80	74	44	93
MRI < 6 months	58	73	37	86
PET < 12 months	57	71	44	80
MRI < 12 months	53	74	47	78

PPV, positive predictive value; NPV, negative predictive value. For other abbreviations see Table 2.

$$(\%)\ \text{PPV calculated as } \frac{\text{total no. of positives} - \text{false-positives}}{\text{total no. of positives}} \times 100;$$

$$(\%)\ \text{NPV calculated as } \frac{\text{total no. of negatives} - \text{false-negatives}}{\text{total no. of negatives}} \times 100;$$

$$(\%)\ \text{sensitivity calculated as } \frac{\text{no. of positively detected relapses within RM}}{\text{total no. of relapses within RM}} \times 100.$$

similar specificity of 73%. The results of PET in patients with HD were very poor with a sensitivity of 0% and a specificity of 67%. MRI gave marginally better results with a sensitivity of 46% and specificity of 74%.

7 patients with NHL above the diaphragm had a PET scan 2 of whom relapsed within the residual mass. There was 1 false-positive result and no false-negative results, producing a sensitivity of 100% and a specificity of 80%. In 5 patients with the disease below the diaphragm, the sensitivity was 67% and the specificity was 50%. The PET scan was positive in 3, of which 1 was a false-positive.

Patients were also analysed for relapse within 12 months of the scan. PET gave a sensitivity of 57% and a specificity of 71%. The PPV and NPV were 44% and 80%, respectively. For MRI the sensitivity and specificity were 53% and 74%. The PPV was 47% with a NPV of 78%.

The predictive value for both tests failed to reach statistical significance. The *P* value for a positive or negative MRI predicting relapse was 0.14 and for PET it was 0.64. Subgroup analysis did not reveal any statistically significant results.

4. Discussion

This study has failed to demonstrate that either MRI or PET is capable of predicting relapse within a residual mass after treatment for lymphoma. The sensitivity of PET for predicting relapse in these patients was only 50%, with a specificity of 69%. However, analysis of certain subgroups, although small and statistically insignificant, are interesting. In the 12 patients with NHL who had a PET scan the sensitivity was 80% with a specificity of 71%. 7 patients had NHL residual masses above the diaphragm and in these, 2 patients relapsed and 5 patients remained disease free. The PET scan was positive in 3 cases, 1 of which was a false-positive. There were no false-negative results. This gave a sensitivity of 100% and a specificity of 80%.

From these results it appears that a negative PET or MRI scan of a residual mass following treatment for lymphoma may have greater clinical utility than a positive result. In the group as a whole there were 15 negative PET results. Of these only four were false-negatives, with a NPV of 73%. This was slightly lower for MRI with a result of 68%. This compares with five false-positives out of nine positive scans producing a PPV of only 44% for PET. For MRI the results are equally poor with a PPV of 53%. In patients with NHL there was only one false-negative PET result from a total of six negative PET scans. The NPV was 83%.

There are a number of both *in vitro* and *in vivo* studies that help to explain the high rate of false-positive results (and thus poor sensitivity and PPV) in the PET scans. Acute inflammatory lesions can accumulate ^{18}FDG and so may be confused with malignant tissue [21]. Kubota and colleagues [22] used autoradiography to study the intratumoral distribution of FDG in mice. They found that macrophages and granulation tissue surrounding necrotic areas in tumours had a greater uptake than viable cancer cells. Radiotherapy can induce inflammatory changes in treated tissues. Several studies have shown that FDG uptake is enhanced by radiotherapy [23,24]. Haberkorn and associates [23] found that FDG did not disappear in most of the colorectal tumours receiving radiotherapy that they studied. They speculated that ^{18}FDG uptake was secondary to inflammation caused by radiotherapy. Engenhart and coworkers [24] found that in colorectal cancers receiving radiotherapy, the uptake of FDG may be increased for several months. Information on changes following chemotherapy however is limited. Haberkorn and associates [25] treated the breast cancer cell line MCF7 with hexadecylphosphocholine (HPC). Six hours following the initiation of chemotherapy they found increased tumour metabolism. In an animal model with implanted breast tumours they found increased ^{18}FDG uptake in 70% of the animals studied at both 1 and 7 days after chemotherapy. Minn and colleagues [26] showed an enhancement of ^{18}FDG uptake following treatment of Lewis lung cancer with doxorubicin. Strauss and coworkers [27] reported a case of primary bone marrow NHL in which the effects of chemotherapy on ^{18}FDG uptake persisted for at least 3 years.

MRI can also produce false-positive results in T2-weighted scans [17]. Causes may include retained secretions after radiation, fat interspersed with fibrosis and inflammatory changes within the residual mass. Assessments revealing active disease more than 6 months after therapy appear more reliable than those performed earlier [17], but are of limited value in a clinical setting where immediate treatment would normally be indicated in the presence of residual disease.

There are other limitations of this study that may explain the poor sensitivity of the PET scanner. Firstly, this is a heterogeneous group of patients with varying histologies and grades. ^{18}FDG uptake has been shown to vary according to tumour grade in different tumours including lymphoma [28]. It is quite conceivable that a lymphoma of lower histological grade would be less likely to have ^{18}FDG uptake but may well relapse if left untreated, increasing the possibility of a false-negative result. The PET scanner used was not a state-of-the-art machine and results with a modern commercial machine, with improved sensitivity and resolution, would have been superior. It must also be noted that the results from this PET scanner are being compared with the results obtained from a modern MRI scanner.

At present there is no conclusive evidence that either MRI or PET can reliably predict relapse within a resid-

ual mass after treatment for lymphoma. However, it does appear that a negative PET or MRI scan may be associated with a favourable outcome. This is consistent with previous studies. De Wit and coworkers [29] studied patients with residual masses following treatment for lymphoma. Of the 32 patients studied 17 (53%) had a negative PET scan at the end of treatment. None of these patients relapsed although the follow-up period was short, with a median of 62.6 weeks (range: 4–102). Bangerter and associates performed PET scans in 36 patients with residual masses. 25 out of 27 patients with negative scans (93%) remained in complete response at 25 months. Of the patients with a positive scan, 4 out of 9 (44%) remained in complete remission [30].

A negative PET scan or MRI of a lymphoma residual mass following therapy may, therefore, make a useful contribution in the clinical decision to avoid further chemotherapy or radiotherapy in patients who have a negative PET scan, in whom these treatment modalities may result in morbidity. From these results it is not clear whether PET is superior to MRI in this setting and additional research is required, including the optimum timing of scans following therapy.

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