Chapter 5

FDG PET versus ^{67}Ga scintigraphy as prognostic test during chemotherapy for non hodgkin's lymphoma

Josée M. Zijlstra, Otto S. Hoekstra, Pieter G.H.M. Raijmakers, Emile F.I. Comans, Jacobus J.M. van der Hoeven, Gerrit J.J. Teule, A. Roelof Jonkhoff, Harm v Tinteren, Adriaan A. Lammertsma, Peter C. Huijgens.

ABSTRACT

For response monitoring of aggressive non-Hodgkin's lymphoma during treatment, a prospective study was performed comparing gallium scintigraphy (^{67}Ga) and positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose (FDG). In 26 patients ^{67}Ga and FDG scans were performed following two cycles of CHOP.Scans were reviewed by 4 experienced nuclear physicians, independently and blinded for the alternative scan technique and follow-up. Eleven out of 26 patients remained free from progression with a mean follow up of 25 $\pm$ 5 months, while 14 patients relapsed and one died of lung cancer. Interobserver variation was significantly greater for ^{67}Ga than for FDG PET. 64% of patients who had a negative early restaging FDG PET remained free from progression versus 50% of patients with negative ^{67}Ga scans. Only 25% of patients with positive PET remained disease free versus 42% of ^{67}Ga-positive patients. Time to progression was associated with the results of ^{18}FDG PET, but not with ^{67}Ga. For the evaluation of early response, FDG PET had better test characteristics than ^{67}Ga.

INTRODUCTION

Less than half of newly diagnosed patients with aggressive non-Hodgkin's lymphoma (NHL) are cured with CHOP-like chemotherapy [1-3]. Patients who respond more rapidly to this front-line chemotherapy have a better and more durable response than slow responding patients [4;5]. Therefore, it is important to distinguish between patients who can be cured with standard approaches and those who may benefit from more intensive treatment.

During and early after therapy, the conventional anatomically oriented radiological methods do not accurately predict patient outcome, mainly due to incomplete or delayed shrinkage of malignant tissues [6-8]. Several studies have shown that CT scans during treatment did not distinguish patients who continued to have complete response at follow-up from those who relapsed [5;9].

^{67}Gallium citrate scintigraphy (^{67}Ga) has been used to classify residual masses in patients after standard induction chemotherapy [10;11]. ^{67}Ga binds to the transferrin receptor which is abundantly present in rapidly growing tissues. The value of early restaging with ^{67}Ga was demonstrated in a selected group of 30 patients with aggressive non-Hodgkin's lymphoma and poor-prognosis, treated with high-dose chemotherapy [2]. Patients with a ^{67}Ga-positive scan midway through chemotherapy had a much poorer outcome than those with a ^{67}Ga-negative scan.

Recently, whole-body positron emission tomography (PET) using ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) has been introduced in the diagnosis and management of malignant lymphoma. Like ^{67}Ga scintigraphy, it offers the possibility of differentiating viable tumour from inert residual masses [12;13]. Malignant tissue is characterised by an enhanced rate of glycolysis due to both increased expression of glucose transporter proteins at the tumour cell surface and increased hexokinase activity [14]. Compared with ^{67}Ga, ^{18}FDG has a more favourable biodistribution with much less uptake in liver, bone marrow, spleen and intestines. It is still unknown however, which of these tracers has the highest avidity for lymphoma tissue in vivo. Furthermore, the performance of PET scanners in terms of spatial resolution and sensitivity clearly outweighs that of gamma cameras. On the other hand, ^{67}Ga scintigraphy is more readily available in most centres and cheaper than PET.

If chemotherapy is effective, ^{18}FDG uptake should be markedly diminished or even completely suppressed [15]. The few studies that have addressed the role of ^{18}FDG in defining early response during chemotherapy, have suggested a role for PET in this setting, by showing a decrease in ^{18}FDG uptake prior to volume reduction on conventional imaging [16-19].

To assess which nuclear imaging technique has the best characteristics as a response monitoring tool for aggressive NHL, a prospective study was performed comparing ^{18}FDG PET and ^{67}Ga scintigraphy after 2 cycles of CHOP chemotherapy.

PATIENTS AND METHODS

Patient population

Between January 1998 and March 2000 26 patients with histologically proven aggressive NHL were included in this prospective study. Patients were treated at the department of Hematology, VU Medical Center, Amsterdam, or at the department of Hematology/Oncology, Hospital Amstelveen. Inclusion criteria were a) diffuse large B-cell lymphoma, mantle cell lymphoma, follicle centre lymphoma grade III and anaplastic large cell lymphoma (REAL classification), b) measurable lesion, c) no former treatment for NHL, d) WHO performance 0-2, and e) informed consent. According to the declaration of Helsinki, the protocol was approved by our Ethical Committee.

Treatment and clinical follow-up

Twenty-five patients were treated with standard CHOP that included every-21-day cycles of cyclophosphamide 750 mg/ m^2 iv, doxorubicin 50 mg/ m^2 iv, vincristine 2 mg iv on day 1 and prednisone 100 mg orally on days 1 through 5. One patient received intensified CHOP containing cyclophosphamide 1000 mg/ m^2 iv, doxorubicin 70 mg/ m^2 iv, vincristine 2 mg iv on day 1 and prednisone 100 mg orally on days 1 through 5 every 14 days with support of 300 µg granulocyte colony-stimulating factor (G-CSF) sc. from day 2 through 9. In 23 patients with stage IE or stage II-IV disease, intended treatment was 6-8 cycles of CHOP, versus 3 cycles of CHOP followed by involved field radiotherapy in 3 patients with stage I.
Follow-up evaluation occurred every 3 months by a haematologist and included physical examination and a laboratory work-up. In case of new symptoms or palpable abnormalities follow-up CT-scans were performed. Patients were followed clinically for a minimum of one year or until death.

Radiographic Evaluation

Before therapy, all patients underwent baseline staging studies including standard histological examination of enlarged lymph nodes and bone marrow and CT-scans of chest, abdomen and pelvis. Conventional or spiral CT was performed after the third cycle of CHOP and 4 weeks post-treatment, respectively, after administration of intravenous contrast medium,

using a Somatom Plus (Siemens) at the University hospital in Amsterdam and a Tomoscan CX/S (Philips) in Amstelveen. Thickness of transaxial slices of neck and thorax/ abdomen was 5 and 10 mm, respectively. Treatment response was classified as complete response (CR), unconfirmed complete response (CRu), partial response (PR), no change (NC) or progressive disease (PD) according to standard criteria [20].

^{18}FDG PET and ^{67}Ga Imaging

Two weeks after the second CHOP cycle, ^{18}FDG PET and ^{67}Ga scans were performed. Clinicians remained blinded to the results of these scans to avoid any impact on patient management.

^{18}FDG PET scans were performed using an ECAT HR+ scanner (Siemens/CTI, Knoxville, Tennessee). Patients were required to fast for at least six hours prior to the study. Serum glucose was measured and proved to be < 6.6 mmol/l in all cases. The scan trajectory comprised the inguinal to the cervical region. Emission scans (2D, 5 mins/ bedposition) were started 60 minutes after intravenous administration of 350-420 MBq ^{18}FDG, for a total imaging time of about 45 minutes. Images were reconstructed with an iterative reconstruction algorithm (OSEM, 4 iterations and 16 subiterations), resulting in a spatial resolution of ~7 mm.

Immediately after PET, 185 MBq ^{67}Ga citrate was administered intravenously. After 72 hours, scintigraphy (whole body) was performed using a dual-head gamma camera (ADAC Genesys, Milpitas CA), typically followed by SPECT (chest and/or abdomen, n=24). SPECT images were reconstructed with filtered back projection and a Hanning filter, resulting in a spatial resolution of ~12 mm.

^{18}FDG PET and ^{67}Ga Assessment

^{67}Ga and ^{18}FDG PET images were visually analysed by 4 experienced nuclear medicine physicians. The observers were blinded for clinical outcome, and each physician observed only a single scan modality of each patient. In a first session, they were also blinded for the baseline clinical staging findings. After an interval of at least 3 months, a second session was held in which the sites that were initially involved according to the routine clinical staging procedure were disclosed. Finally, for each patient and each modality a consensus conclusion was formulated by both teams of observers, and this result was used in the analysis of test performance versus outcome.

In the first sessions, regions of abnormal uptake of ^{67}Ga or ^{18}FDG were scored as follows: 0= benign, 1= probably benign, 2= unclear, 3= probably malignant, 4= malignant. In the

final analysis, only abnormal focal tracer uptake was considered in sites clinically known to be involved at presentation. The observers were requested to formulate a final assessment in a consensus reading in one of three categories: positive, equivocal or negative for viable tumour.

Statistical analysis

Interobserver agreement was measured with intra class coefficients (ICC). Agreement between ^{67}Ga and ^{18}FDG PET consensus readings was measured with Cohen's kappa. Time to progression (TTP) was calculated from study entry to the first objective evidence of relapse or progression. Survival curves were estimated by the Kaplan-Meier method [21]). Associations between scan results (^{67}Ga and ^{18}FDG, respectively) and TTP were assessed using the log-rank test.

RESULTS

Response to CHOP therapy

Twenty-six patients (14 male and 12 female) diagnosed with aggressive NHL and treated with CHOP were included. Their median age was 55 years (range 22-77). Patients' characteristics are listed in Table 1.

At standard mid-treatment evaluation (after 3 cycles of CHOP), CT and/ or clinically defined response was considered insufficient (less than 50% tumour regression on CT or progression after initial clinical response) in two patients, resulting in a switch to second line chemotherapy and stem cell transplantation. One of them died after progression during second line chemotherapy, the other is still in complete remission (CR) 30 months after high dose chemotherapy and stem cell transplantation (Fig 1).

At conventional restaging after treatment, 15/26 patients (58 %) achieved CR or undetermined CR (CRu), 9 of whom are still

Table 1. Patient Characteristics (n= 26)

Age, years	
median	55
range	22-77
Sex	
male	14
female	12
Ann Arbour clinical stage	
I	5
II	11
III	4
IV	6
REAL classification	
Diffuse large B-cell	20
Mantle-cell lymphoma	3
Burkitt's lymphoma	1
Follicle-centre lymphoma	2

Abbreviations: REAL, Revised European-American Lymphoma classification

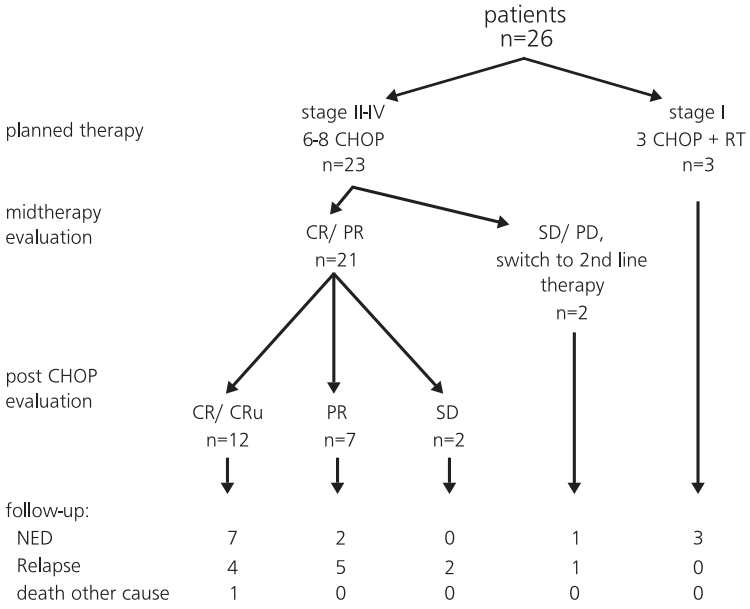

Figure 1. Clinical outcome after treatment with standard evaluation using CT-scans.
Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; NED, no evidence of relapse

in CR with a median follow-up of 25 (range 14-34) months. One of the patients in CR after treatment died due to lung cancer. Seven patients achieved partial remission (PR), and two progressed on therapy after first achieving transient PR. Four of the 15 complete responders and five of the 7 partial responders relapsed within a median of 10 (range 3-17) months following completion of therapy.

Observer variability of ^{18}FDG PET and ^{67}Ga readings

Standard clinical staging prior to CHOP therapy revealed 61 sites involved in 26 patients. When observers were blinded to initial clinical staging findings, interobserver variability was significantly higher with ^{67}Ga than with ^{18}FDG PET (on a lesion basis: ICC ^{67}Ga: 0.53, 95%CI 0.22-0.72, ^{18}FDG-PET: 0.98, 95%CI 0.97-0.99; on a patient basis: 0.67, 95%CI 0.28-0.85, versus 0.98, 95%CI 0.95-0.99, respectively). When initial clinical staging data were made available, interobserver agreement increased for ^{67}Ga (on a lesion basis: 0.80, 95%CI 0.66-0.88; on a patient basis 0.74, 95%CI 0.43-0.88), and remained similar for PET.

^{18}FDG PET and ^{67}Ga scans versus outcome

After 2 cycles of CHOP, 18FDG PET was positive in 12 patients, and negative in 14 (Table 2). Equivocal readings did not occur. In 3 patients, PET showed diffusely enhanced uptake at

Table 2. Clinical outcome related to imaging results

	PET^+ Ga^+	PET^+ Ga^-	PET^- Ga^+	PET^- Ga^-	
Relapse	6*	3	1	4	14
No relapse	2	1	3	6	12
	8	4	4	10	26

* including 1 patient with lung cancer

sites originally not affected at initial (CT) staging. According to protocol, these scans were classified as negative, and the patients remained disease-free at follow-up.

^{67}Ga scintigraphy was positive in 12 patients. One patient showed marginally enhanced uptake at an originally unaffected site, classified as negative and, in retrospect, follow-up did not show recurrent NHL. On a patient basis, results of ^{18}FDG PET and ^{67}Ga scintigraphy were concordant in 18/26 patients (69%).

^{18}FDG positive / ^{67}Ga positive studies (n=8)

Five out of eight patients showing accumulations in both ^{18}FDG PET and ^{67}Ga scintigraphy relapsed within 12 months. Relapse was proven either by biopsy (n=2) or by progressive disease on CT (n=3). All relapses occurred in sites indicated by PET. One patient initially had cervical lymphadenopathy and a lesion in the right lung, which was suspected to be lymphoma too. Following six cycles of CHOP, lymphadenopathy diminished but the lung lesion increased. After lobectomy, this PET-positive site proved to be non-small cell lung cancer. A few months later, the patient died of metastatic lung cancer, without evidence of relapsed NHL. Two patients with positive ^{18}FDG PET and ^{67}Ga scans following the second CHOP are still in continuous remission. However, one of them was treated with 2nd line therapy including stem cell transplantation because of insufficient response on CT at midtreatment evaluation. The other patient is still in clinical remission 29 months after 8 cycles of CHOP without further therapy.

^{18}FDG positive / ^{67}Ga negative studies (n=4)

In this group of four patients, three relapsed at ^{18}FDG positive sites, which were all extra-nodal (lung, liver and bones). The ^{67}Ga scans did not show pathological ^{67}Ga uptake at these sites. The remaining ^{18}FDG positive patient had diffusely enhanced uptake in the right lower lobe of the lung. His baseline CT scan had revealed a hilar mass and a consolidated right lower lobe. It was unclear whether this was pulmonary lymphoma or merely post-obstructive atelectasis with pneumonitis. Follow up of more than two years did not reveal relapsed lymphoma.

^{18}FDG negative / ^{67}Ga positive studies (n=4)

Out of 4 ^{18}FDG negative/ ^{67}Ga positive patients, one relapsed at the ^{67}Ga-positive site, in a lymphnode located near the renal pelvis. An ^{18}FDG hot spot in this area had been interpreted as physiological retention in the renal pyelum (Fig 2). The other three patients with a positive ^{67}Ga scan are still in remission. These scans showed ^{67}Ga avidity in regions that were clinically affected but also known as sites of physiological biodistribution of ^{67}Ga (spleen, tonsil and parotid gland).

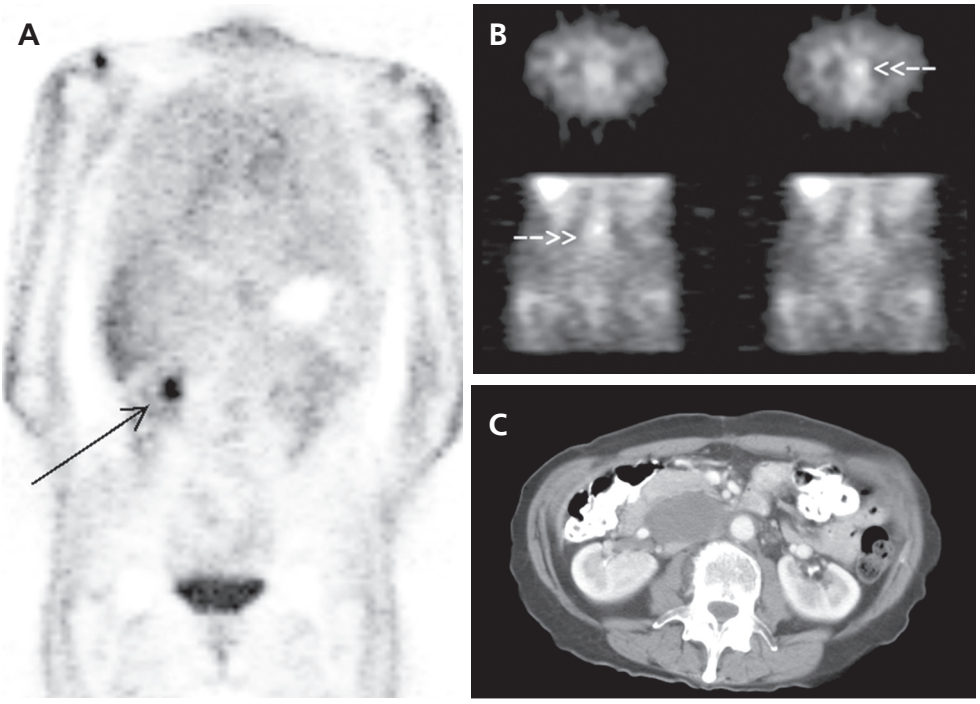

Figure 2. Prognostic value of ^{18}FDG PET and ^{67}Ga in a patient with a positive galliumscintigraphy (SPECT) and a negative PET. The FDG uptake near the renal pyelum was interpreted as physiological retention in the pyelum. The staging CT-scan showed a large mass medial from the right pyelum.

^{18}FDG negative / ^{67}Ga negative studies (n=10)

Six of this subset are in continuous clinical remission, while two experienced a relapse exclusively in the central nervous system. Retrospectively, in one patient abnormal ^{18}FDG uptake was seen in the cervical spinal cord 3 months prior to clinical relapse. Two other patients, both with a mantle cell lymphoma, relapsed 12 and 21 months after CHOP, respectively.

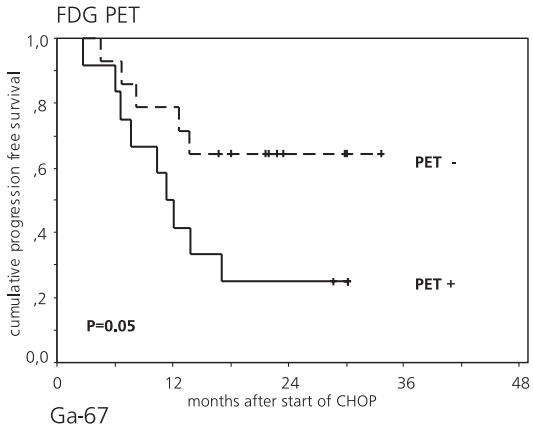

Figure 3. Kaplan-Meier of progression free survival in 12 patients with positive ^{18}FDG PET compared with 14 patients with negative ^{18}FDG PET after 2 CHOP.

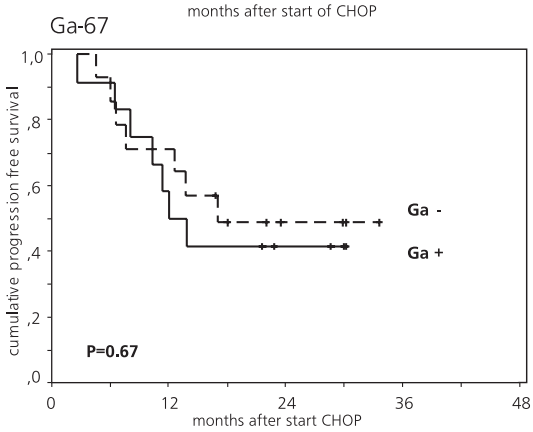

Figure 4. Kaplan-Meier of progression free survival in 12 patients with positive ^{67}Ga compared with 14 patients with negative ^{67}Ga after 2 CHOP.

At a median follow-up of 16 months (range 2-33), 64% of patients who had a negative early restaging ^{18}FDG PET remained in clinical remission, whereas only 25% of patients with a positive PET scan remained disease-free. However, ^{67}Ga scans at that time-point appeared to have no predictive value for treatment outcome (50% and 42%, respectively).

The Kaplan Meier curves for time to progression of patients with a negative or positive ^{18}FDG PET or ^{67}Ga scan are shown in Figure 3 and 4, respectively. The results of ^{18}FDG PET after only two cycles of CHOP are significantly related to the time to progression after first-line treatment (log rank P-value=0.05). ^{67}Ga scan results did not show any relation with the time to progression (log rank P-value=0.67).

DISCUSSION

The present study is, to our knowledge, the first head-to-head comparison of ^{67}Ga scintigraphy and ^{18}FDG PET in a cohort of NHL patients evaluated early during CHOP treatment. In this study, interobserver agreement and prognostic value of ^{18}FDG PET were clearly better than

those of ^{67}Ga scintigraphy. Early recognition of patients who will fail to respond to first-line chemotherapy or who will relapse shortly after achieving a partial or complete remission is important, because these patients could be candidates for immediate more intensive treatment rather than continuation of ineffective front-line chemotherapy with unnecessary toxicity. Midtreatment CT-scans do not accurately discriminate between patients who will achieve durable CR and those who will relapse [5;11]. Whilst assessment of response by CT largely depends on reduction in size of enlarged lymphadenopathy, functional imaging reflects the metabolic activity of tissues. Conceptually, this phenomenon may be more accurate in assessing treatment response than anatomical changes on CT. Furthermore, metabolic changes following therapy tend to precede anatomical changes and allow early response evaluation [16;22].

Even though several other tracers have been proposed for use in malignant lymphoma (^{99m}Tc-MIBI, ^{201}Tl, ^{111}In-octreotide), most data are available for ^{67}Ga and ^{18}FDG. ^{67}Ga imaging is useful for monitoring response or for detection of recurrence in lymphoma, especially above the diaphragm. Limitations are the low sensitivity and spatial resolution of gamma cameras and the physiological distribution of ^{67}Ga. This may compromise abdominal evaluation and require additional imaging, which is inconvenient in settings where rapid decisions have to be made as is the case with monitoring response in ongoing chemotherapy.
Evidence in support of ^{67}Ga came from two recent studies. Janicek et al. [2] prospectively evaluated 30 patients with bulky advanced-stage aggressive NHL and poor prognosis with ^{67}Ga scans at baseline and following two cycles of high dose CHOP containing cyclophosphamide 4 g/m^2 and doxorubicin 70 mg/m^2. After a median follow up of 31 months, 94% of patients with negative early restaging ^{67}Ga scans remained free from progression, versus only 18% of those with positive scans. However, these results were achieved in a highly selected group of patients treated with high dose CHOP, which is not representative for all NHL patients treated with standard-dose CHOP. In another prospective study of 64 patients with aggressive NHL, a negative ^{67}Ga after the first cycle of CHOP or CHOP-like chemotherapy predicted long-term continuous CR in 83% of patients. A positive ^{67}Ga after one cycle predicted treatment failure in 64% of patients [23]. They concluded that a positive ^{67}Ga early during treatment might be used as an independent test in selecting patients who will not respond favourably to current treatment for early therapeutic modifications.

Despite the important role of ^{67}Ga in lymphoma imaging, ^{18}FDG PET might be a more effective tool, because of the inherent superiority of PET scanners over standard gamma cameras [24] and the more favourable biodistribution of ^{18}FDG compared to ^{67}Gallium. High

avidity of ^{18}FDG has been described for most types of lymphomas [25;26]. Finally, ^{18}FDG PET is a single day procedure, and radiation exposure is considerably less than with typical dosages of ^{67}Gallium. It is known for a decade that changes of ^{18}FDG uptake can be observed within days after start of therapy [16;19].

A few studies with smaller number of patients have shown that the evaluation of ^{18}FDG uptake by lymphoma early during chemotherapy can predict the response to treatment. In a quantitative study, Romer et al. [19] reported that standard chemotherapy in 11 patients caused a rapid decrease of tumour ^{18}FDG uptake as early as 7 days after treatment. The mean metabolic rates for ^{18}FDG 7 days after initiation of chemotherapy were significantly lower in 6 of 11 patients still in CR after a follow-up of 16 months. However, ^{18}FDG uptake at 42 days was even better for predicting long-term outcome. In a heterogeneous study population of 28 patients with NHL, treated with different poly-chemotherapy regimens, Jerusalem et al. [27] reported that persistent ^{18}FDG uptake after 2-5 cycles was predictive of CR, progression free survival and overall survival. All five patients with, and 7 out of 21 patients without residual abnormal ^{18}FDG uptake, relapsed or progressed. In their study, the sensitivity of qualitative ^{18}FDG PET imaging in identifying patients with a poor outcome was insufficient. Recently, Spaepen et al. have assessed the value of midtreatment ^{18}FDG PET in predicting clinical outcome in 70 patients with aggressive NHL. The authors concluded that midtreatment restaging ^{18}FDG PET scans were highly predictive for progression free and overall survival ($p< 0.00001$) [28].

Since visual analysis is the standard approach in this application, observer variability is an important issue, as has been shown for CT scan [29]. However, interobserver variation has not been thoroughly investigated for either tracer. In the present study, interobserver agreement was clearly better for ^{18}FDG PET. Since all observers had extensive experience with both techniques, this supports the notion that reading of ^{67}Ga scans is relatively complex [30]. In part, this is explained by its biodistribution. In addition, it is likely that the image quality of ^{67}Ga SPECT images versus ^{18}FDG PET contributes to the observed differences. In this study, ^{67}Ga doses as recommended in the Netherlands were used. It cannot be excluded that higher doses (e.g. 370 MBq) would have improved the test performance. The present data suggest that additional clinical data improve interrater performance with ^{67}Ga.

In this study, scan data were compared with initial clinical staging. Additional baseline scans would have been useful, but prior to this study it was anticipated that this would sincerely compromise patient compliance since neither procedure is standard for staging in our clinical setting. Moreover, ^{67}Ga scintigraphy does not contribute to conventional clinical staging [31;32]. This is not necessarily the case for ^{18}FDG PET [33;34]. However, in retrospect, no recurrence

became manifest in clinically unsuspected areas designated as abnormal on ^{18}FDG PET or ^{67}Ga scans, except for a clinically unknown meningeal localisation which was retrospectively identified at ^{18}FDG PET.

The primary aim of the present study was to compare two scintigraphic methods. Obviously, the sample size was too small to provide accurate estimates of predictive values. However, the results of ^{18}FDG PET after only two cycles of CHOP are strongly related to the time to progression after first-line treatment (log rank p-value=0.05). ^{18}FDG PET had clearly better test characteristics than ^{67}Ga scintigraphy in the evaluation of early response. More precise estimates of predictive values of ^{67}Ga scintigraphyand ^{18}FDG PET can be obtained from a larger observational study. Alternatively, the impact of application of either technique on a patient outcome level would require a randomised study of^{67}Ga versus ^{18}FDG PET in this context. The congregated evidence on ^{18}FDG PET and early response monitoring suggests that a randomised trial is now appropriate to decide whether implementation of ^{18}FDG PET in clinical management will improve patient outcome.

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