Positron emission tomography with [18F]FDG for therapy response monitoring in lymphoma patients

Karoline Spaepen[1], Sigrid Stroobants[1], Gregor Verhoef[2], Luc Mortelmans[1]

[1] Department of Nuclear Medicine, UZ Gasthuisberg, Leuven, Belgium
[2] Department of Hematology, UZ Gasthuisberg, Leuven, Belgium

Published online: 23 April 2003

Abstract. Lymphomas are a heterogeneous group of diseases with differing histopathology, clinical behaviour, response to therapy and outcome. Lymphomas are highly sensitive to chemotherapy and radiotherapy, and the recent developments in treatment have considerably improved clinical outcome. However, there is increasing recognition that this has been at the cost of long-term treatment-related effects in a relatively young patient population. Thus, one of the most challenging aspects in the imaging of lymphoma patients is tailoring the intensity of the treatment to the individual patient. This paper reviews recently published data concerning the use of fluorine-18 fluorodeoxyglucose positron emission tomography ([18F]FDG-PET) for therapy monitoring in lymphoma patients and highlights the shortcomings and future directions. A temporary strategy for the implementation of [18F]FDG-PET in the management of lymphoma patients is proposed.

Keywords: [18F]FDG-PET – Lymphoma – Predictive value – Response monitoring

Eur J Nucl Med Mol Imaging (2003) 30 (Suppl. 1): S97–S105
DOI 10.1007/s00259-003-1166-5

Introduction

Lymphomas are a heterogeneous group of diseases which differ with regard to histopathology, clinical behaviour, response to therapy and outcome. In contrast to many solid tumours, lymphomas are highly sensitive to chemotherapy and radiotherapy and the recent developments in treatment have considerably improved clinical outcome. It is increasingly recognised, however, that this success is achieved at the cost of long-term treatment-related effects in a relatively young patient population. Thus, one of the most challenging aspects in the imaging of lymphoma patients is tailoring the intensity of the treatment to the individual patient. Fluorine-18 fluorodeoxyglucose positron emission tomography ([18F]FDG-PET), using increased glycolysis to differentiate between fibrosis and active tumour, was first reported by Paul [1] as a functional imaging technique for the detection of lymphomas. During recent years, several studies [2] have shown the effectiveness of [18F]FDG-PET in the post-treatment evaluation of lymphomas and reported that it has a high predictive value for the differentiation between active tumour and fibrosis in patients with a residual radiological mass. Studies involving the sole use of [18F]FDG-PET (as an alternative to conventional diagnostic methods), and performed in order to assess the prognostic role of [18F]FDG-PET during or after first-line treatment, during high-dose chemotherapy with stem cell transplantation and in the setting of radioimmunotherapy, have to date been performed in only a small number of patients. The aim of this paper is to review recently published data concerning therapy monitoring in lymphoma patients and to highlight the shortcomings and future directions. Finally, a temporary strategy for the implementation of [18F]FDG-PET in the management of lymphoma patients is proposed.

Luc Mortelmans (✉)
Department of Nuclear Medicine, UZ Gasthuisberg,
Herestraat 49, 3000 Leuven, Belgium
e-mail: Luc.Mortelmans@uz.kuleuven.ac.be
Tel.: +32-16-343715, Fax: +32-16-343759

Predicting response after first-line treatment

Obtaining a complete remission (CR) after first-line chemotherapy is the main objective in lymphoma patients as it is usually associated with a longer progression-free survival (PFS) and a better clinical outcome than is partial remission (PR) [3]. Structural imaging tools require perturbation or enlargement of anatomical structure to suggest tumour, and initially enlarged tumour sites may remain enlarged without any tumour activity owing to the development of fibrosis and/or tumour necrosis. Re-

Table 1. Summary of the results reported in the literature concerning the use of [^{18}F]FDG-PET for therapy response monitoring in lymphoma patients

Authors/ indication	Article type	No. of patients	Population	Specifications	FU (months)	PFS PET+ vs PET–	OS PET+ vs PET–
End of therapy							
Mixed population							
Zinzani et al. [9]	ra	44	HD/NHL	Abdominal involvement in all	20	1 yr: 15% vs 95%, 2 yr: 0% vs 95%	
Jerusalem et al. [10]	ra	54	HD/NHL	Residual mass in 24	21	1 yr: 0% vs 86%	1 yr: 50% vs 92%
Maisey et al. [11] (NDP)	ra	24	HD/NHL	Residual mass in all	29	56% vs 73%	
NHL							
Mikhaeel et al. [13]	ra	45	Aggr. NHL	Residual mass in 17	30	1 yr: 0% vs 83%	
Spaepen et al. [14]	ra	93	Aggr. NHL	Residual mass in 24	22	2 yr: 4% vs 85%	
Juweid et al. [15]	a	38	Aggr. NHL		15.5	1 yr: 8% vs 88%	
HD							
de Wit et al. [17]	ra	37	HD	Residual mass in all	25.6	54% vs 96%	
Weihrauch et al. [18]	ra	28	HD	Residual mass in all	28	1 yr: 40% vs 95%	
Spaepen et al. [19]	ra	60	HD	Residual mass in 43	31	2 yr: 4% vs 85%	
Mikhaeel et al. [20])	a	65	HD		36	1 yr: 0% vs 93%	
Interim							
Hoekstra et al. [24]	ra	11	HD/NHL	Pilot study	NA		
Dimitrakopoulou–Strauss et al. [25]	ra	10	HD/NHL	Pilot study	NA		
Römer et al. [26]	ra	11	Aggr. NHL	Pilot study	NA		
Jerusalem et al. [27]	ra	28	Aggr. NHL	After 2–3 cycles	28	1 yr: 20% vs 81%, 2 yr: 0% vs 62%	1 yr: 20% vs 87%, 2 yr: 0% vs 68%
Spaepen et al. [28]	ra	70	Aggr. NHL	After 3–4 cycles	36	1 yr: 10% vs 92%, 2 yr: 4% vs 85%	1 yr: 60% vs 100%, 2 yr: 40% vs 95%
Mikhaael et al. [13]	ra	23	Aggr. NHL	After 2–4 cycles	30	12% vs 100%	
Mikhaeel et al. [20]	a	32	HD	After 2–4 cycles	36	1 yr: 0% vs 92%	
Kostakoglu et al. [29] (NDP)	ra	23	HD/NHL	After 1 cycle/ at the end	19	1 yr: 13% vs 87% (at interim), 17% vs 65% (at the end)	
Pretransplantation							
Becherer et al. [33]	ra	16	HD/NHL	8 weeks before ASCT	17	1 yr: 18% vs 100%	1 yr: 55% vs100%
Cremerius et al. [35]	ra	22	NHL	Sequential	25	1 yr: 28% vs 72% (before transplantation)	1 yr: 57% vs 87%
Filmont et al. [34]	a	21	HD/NHL	Before ASCT	13.3	1 yr: 25% vs 94%	
Schot et al. ([36]	a	34	HD/NHL	After 2 courses of chemotherapy	16.8	48% vs 78%	
Immunotherapy							
Torizuka et al. [37]	ra	14	Low-grade NHL	Before, after 6–7 days and after 33–70 days	?	PET 1–2 months after therapy correlated with response	
Scheidhauer et al. [38]	a	22	NHL	Before and after 6 weeks	18	Rapid decline correlated with response	
Hofmann et al. [39]	a	15	Aggr. NHL	Before and after 4–6 weeks	?	Less than 25% SUV reduction: poor prognosis	

ra, Research article; a, abstract; FU, follow-up; PFS, progression-free survival; OS, overall survival; Aggr., aggressive; ASCT, autologous stem cell transplantation; NDP, non-dedicated PET

cently, international experts have tried to refine the criteria defining a complete response. Because of the uncertainty in the definition of a CR, a new category of response, CRu (complete remission unconfirmed), has been created to reflect the unknown significance of persisting radiological abnormalities in patients who otherwise seem to be in CR. Despite the introduction of high-resolution CT, it is still the case that morphological imaging modalities cannot reliably predict the clinical outcome after therapy [4], and magnetic resonance imaging (MRI) has not proved more useful than CT imaging [5]. Gallium-67 single-photon emission tomography (^{67}Ga-SPET) is routinely used for the evaluation of residual masses after chemotherapy and has been shown to be very promising in the monitoring of disease response [6, 7, 8]. Despite the important role of ^{67}Ga scintigraphy, [^{18}F]FDG-PET seems to be a more favourable technique because of the inherent superior resolution and sensitivity of PET imaging methods and the fact that they permit better interpretation of the abdomen. Moreover, the long half-life of 78 h for ^{67}Ga results in a radiation burden of 44 mSv per examination using a standard dose of 370 MBq, and imaging is usually performed 48–96 h after administration. In contrast, [^{18}F]FDG-PET entails a radiation burden of about 10 mSv per study and requires a maximum examination time of 2 h. The literature concerning the post-treatment evaluation of lymphoma patients using [^{18}F]FDG-PET includes both studies with combined analyses of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) (despite their clearly different histopathology, treatment and prognosis) and studies with separate analyses of these disease entities. Table 1 summarises the results of the various studies, which are discussed in more detail below.

Combined population of NHL and HD patients

Zinzani et al. [9] reported a high predictive value of [^{18}F]FDG-PET for the differentiation between active tumour and fibrosis in 44 lymphoma patients, all with abdominal involvement before the start of treatment. After treatment, seven patients had negative PET and CT and none of them relapsed. The remaining 37 patients had positive CT findings. In this group, 13 patients with a positive PET relapsed, whereas only one relapse occurred in the PET-negative group. The 2-years PFS was 95% for the PET-negative group and 0% for the PET-positive group.

Jerusalem et al. [10] compared the prognostic role of [^{18}F]FDG-PET and CT after first-line treatment in 54 NHL/HD patients. [^{18}F]FDG-PET had a higher diagnostic and prognostic value than CT in the post-treatment evaluation of lymphomas (positive predictive value 100% vs 42%). The 1-year PFS and overall survival (OS) were 86% and 92% for the PET-negative group and 0% and 50% for the PET-positive group respectively.

Maisey et al. [11] compared [^{18}F]FDG-PET with MRI in the differentiation between active tumour and fibrosis in 22 patients. No statistically significant difference was found in the predictive value of [^{18}F]FDG-PET and MRI. In this respect, the findings contradict the previous reports. The discrepancy may be due to the fact that the PET scanner used for this study was not a state of the art machine, which might have rendered the results less sensitive.

Non-Hodgkin's lymphoma

Although response to therapy and clinical outcome have been considerably improved by the use of doxorubucin-containing chemotherapy regimens, less than half of patients with newly diagnosed aggressive NHL can be cured with standard induction therapy [12]. The main question in the post-therapy evaluation of NHL patients is: Can [^{18}F]FDG-PET identify those patients with insufficient response to treatment and, thus, poorer clinical outcome?

Mikhaeel et al. [13] compared [^{18}F]FDG-PET with CT as a prognostic indicator in the treatment of aggressive NHL. [^{18}F]FDG-PET was more accurate than CT in assessing remission status following treatment. The relapse rate was 100% for positive PET and only 17% for negative PET, compared with 41% and 25% for patients with positive and negative CT respectively. The 1-year PFS was 0% for the PET-positive group compared with 83% for the PET-negative group.

In 93 NHL patients undergoing first-line chemotherapy, Spaepen et al. [14] reported that [^{18}F]FDG-PET had a high predictive value for the detection of residual or recurrent disease. PFS was shorter for patients who had persistent [^{18}F]FDG uptake. All patients with persistent uptake suffered disease relapse. The 2-year actuarial PFS rate for PET-negative patients was 85%, as compared with 4% for PET-positive patients.

Recently, Juweid et al. [15] confirmed these findings in 38 patients with aggressive NHL. The positive and negative predictive values of [^{18}F]FDG-PET for 1-year PFS were 92% and 88% respectively, compared with 47% and 85% for CT.

To summarise, persistent abnormal [^{18}F]FDG uptake in initially involved sites is highly predictive for residual or recurrent disease. If abnormal [^{18}F]FDG uptake is seen outside the initially involved sites, infectious/inflammatory lesions and thymic hyperplasia first have to be excluded. A negative result, however, cannot exclude minimal residual disease, and late relapses after a negative PET result are possible. It is important to mention that all these studies included only cases of aggressive NHL, mostly after first-line chemotherapy. Separate analyses are necessary for low-grade lymphomas since [^{18}F]FDG-PET appears to be of less value in such cases, frequently failing to demonstrate disease seen on con-

ventional imaging in the pre-treatment evaluation, which could hamper the interpretation of post-treatment scans. Moreover, strictly extrapolating the conclusions of aggressive to low-grade lymphomas is difficult, since they have different cure rates and different treatment options.

Hodgkin's disease

Hodgkin's disease is one of the few adult malignancies that in most instances can be successfully treated. Compared with NHL patients, most patients with HD are younger, present more often with stage I–III disease and are usually treated with combination chemo-radiotherapy [16]. Curative strategies are dependent on adaptation of therapy according to the treatment response; the ultimate goal is cure of all patients without inducing secondary malignancies or cardiovascular disease. Although response rates are high in HD patients, residual masses are more frequent than in NHL and the negative predictive value of [^{18}F]FDG-PET at the end of treatment is very important. Because of early and late toxicity, treatment in these patients should be limited to a minimum, without compromising the clinical outcome.

Two studies evaluated the predictive role of [^{18}F]FDG-PET in HD patients with a residual mass at the end of treatment. de Wit et al. [17] investigated 37 HD patients with a residual mass. A total of 50 [^{18}F]FDG-PET scans were included before and after additional radiotherapy. [^{18}F]FDG-PET showed promising sensitivity, specificity, PPV, NPV and accuracy of 91%, 69%, 46%, 96% and 74%, respectively, with respect to the prediction of disease-free survival. The authors reported a high number of false positive studies. However, six patients underwent [^{18}F]FDG-PET prior to the additional radiotherapy, and residual lymphoma could have been the cause for thes so-called false positive [^{18}F]FDG uptake. The study by Weihrauch et al. [18] included 28 HD patients with a residual mass at the end of treatment and no patient received another treatment before the remission status was documented in order to preserve the predictive value. The 1-year PFS was 95% for the PET-negative group versus 40% for the PET-positive group. Although this study reported fewer false positive results, the data indicate that one should not exclusively rely on a positive [^{18}F]FDG-PET result; inflammation or infections have to be ruled out, especially when pathological [^{18}F]FDG uptake is seen outside the initially involved sites.

Spaepen et al. [19] published a study concerning 60 HD patients who underwent [^{18}F]FDG-PET at the end of first-line treatment with or without a residual mass. The 2-year disease-free survival was 4% for the positive group and 85% for the negative group, findings comparable to those of their study on NHL patients. Mikhaeel et al. [20] confirmed these findings in 65 HD patients, with a 1-year PFS of 0% versus 93%.

In conclusion, [^{18}F]FDG-PET could be the standard procedure in routine clinical circumstances for the evaluation of patients with HD after first-line therapy. However, some pertinent questions about the role of [^{18}F]FDG-PET have not yet been fully answered. First, the PFS after positive [^{18}F]FDG-PET varies between 0% and 54% depending on the study population. In young patients with a residual mass who have an [^{18}F]FDG-PET scan after the administration of radiotherapy, false positive results seem to be more common owing to inflammation and thymic hyperplasia. A pre-treatment scan can be helpful in resolving some equivocal results. Secondly, in the study of Spaepen et al. [19], all patients with early stage HD had a negative [^{18}F]FDG-PET scan after first-line treatment and none of these patients relapsed. Therefore, the clinical value of [^{18}F]FDG-PET in this group is controversial. On the one hand, a good outcome in early stage HD patients does not so much prove the predictive value of a negative scan as much as it confirms the excellent prognosis in this group. On the other hand, only a small number of HD patients have no residual mass on CT, and so defining a complete response and predicting outcome on the basis of conventional radiological modalities remains difficult. Finally, until now there have been no prospective studies investigating the role of [^{18}F]FDG-PET for guiding radiotherapy in HD patients. Current trials are evaluating the use of shortened courses of chemotherapy, chemotherapy combined with smaller radiation fields or lower radiation doses and chemotherapy without radiation therapy in order to avoid long-term toxicities without compromising the cure rate in patients with HD. [^{18}F]FDG-PET should be added as a standard procedure in these trials and large multicentre prospective studies in order to establish its role firmly and to help refine the current treatment protocols.

Early response assessment

Since more aggressive but also more toxic treatment modalities are available, there is growing interest in the therapy monitoring of patients with aggressive lymphoma. Since 1993, the International Prognostic Index (IPI) [21] has been used to summarise different prognostic clinical factors at presentation and has become an established parameter for risk stratification. The clinical features incorporated in the IPI reflect the biological heterogeneity of aggressive NHL. However, the duration of CR, and thus the long-term clinical outcome, might be significantly more affected by the sensitivity of the tumour to the chemotherapy than by the clinical prognostic factors at presentation, and further prognostication of outcome early during treatment, leading to a rapid change of therapy, might improve outcome and survival. Armitage et al. [22] reported that patients with a rapid response to induction treatment are likely to have a better and more durable response than patients who achieve

a CR more slowly. Until now, morphological imaging modalities (CT and MRI) using sequential determination of tumour size have been performed to assess the tumour response induced by chemotherapy. However, tumour volume reduction is only a late sign of effective therapy [23], and several courses of chemotherapy are frequently required before it can be determined whether the treatment is effective. Using CT findings as a criterion for early response may cause an unacceptable number of patients to be labelled as poor responders and expose them to more aggressive or experimental therapy, even if these patients could have achieved a durable complete response with the installed chemotherapy.

The studies of Hoekstra et al. [24] and Dimitrakopoulou-Strauss et al. [25] have shown that the decrease in [^{18}F]FDG uptake in NHL during chemotherapy does reflect treatment-induced metabolic changes rather than partial volume effects or therapy-induced changes in blood glucose levels. Römer et al. [26] documented the extent and time course of changes in [^{18}F]FDG metabolism in response to chemotherapy in 11 patients. Standard induction chemotherapy in NHL caused a rapid decrease in [^{18}F]FDG uptake as early as 7 days after treatment. However, [^{18}F]FDG uptake at 42 days correlated better with long-term outcome than the 7-day parameter.

The first larger clinical study of 28 patients who underwent an [^{18}F]FDG-PET scan after a median of three cycles of polychemotherapy was presented by Jerusalem et al. [27]. Persistent abnormal uptake after a few cycles of chemotherapy was predictive of PFS and OS at the end of treatment. The main disadvantages of this study were the rather small number of patients and, more importantly, the heterogeneity of the population, which included not only patients with newly diagnosed aggressive NHL but also patients with low-grade or relapsing NHL, who clearly have different outcomes and require different treatment protocols.

Mikhaeel et al. [13] published a study on 23 patients with aggressive NHL who had an interim scan after two to four cycles of chemotherapy. The interim scan provided valuable information regarding early assessment of response and long-term prognosis, with no relapses in patients with no or minimal residual disease compared with an 87.5% relapse rate in those with persistent PET activity. The same group investigated the role of an interim scan (after two or three cycles) in 32 HD patients [20]. They found a relapse rate of 100% for the [^{18}F]FDG-PET positive group compared with 8% for the negative group.

The first study in a larger patient population to compare the interim [^{18}F]FDG-PET scan with the IPI was presented by Spaepen et al. [28]. Of the 70 patients with aggressive NHL who were prospectively enrolled after three or four cycles of chemotherapy, 33 showed persistent abnormal [^{18}F]FDG uptake and none of these patients achieved a durable CR. By contrast, 31 of the 37 patients with a negative scan remained in CR at a median follow-up of 1,107 days. Only 6 of these 37 patients either achieved only a PR or relapsed. Comparison between the groups indicated a statistically significant association between [^{18}F]FDG-PET findings and PFS ($P<0.00001$) and OS ($P<0.00001$). In multivariate analysis, [^{18}F]FDG-PET at mid-treatment was a stronger prognostic factor for PFS ($P<0.0000001$) and OS ($P<0.000009$) than was the IPI ($P<0.58$ and $P<0.03$ respectively).

Kostakoglu et al. [29] recently published a study regarding the prognostic role of an [^{18}F]FDG-PET scan after one cycle of chemotherapy and compared this with the post-treatment scan. In 23 patients, a statistically significant difference in PFS between those with positive and negative [^{18}F]FDG-PET results was obtained both after the first cycle and at the completion of therapy. The PFS and [^{18}F]FDG-PET results obtained after the first cycle correlated better than those obtained after the completion of chemotherapy ($r^2=0.45$ vs 0.17). [^{18}F]FDG-PET had greater sensitivity and positive predictive value after the first cycle (82% vs 45.5% and 90% vs 83%, respectively) than after the last cycle. These results are similar to other studies for early response monitoring but dramatically less optimal for post-therapy assessment. In an invited commentary, Lowe and Wiseman [30] analysed the data in light of a few important variables that may explain these differences. Firstly, trial patients had different diseases, were being treated differently and were at different time points in their treatment. Secondly, for a prospective trial conducted at a large referral centre and open for 3.5 years, the number of consecutive patients enrolled, 23, was rather low. Thirdly and most importantly, a coincidence PET camera was used for the detection of subtle disease persistence, especially after treatment. The disease sensitivity of dedicated PET cameras is well known to surpass that of coincidence PET scanners, even with the use of attenuation correction.

In conclusion, there are promising data suggesting that the results of early restaging [^{18}F]FDG-PET are an important prognostic factor and may be used to tailor induction chemotherapy in patients with aggressive NHL and HD. If [^{18}F]FDG-PET findings remain positive at mid-treatment, these poor-prognosis patients may benefit from an early change in therapeutic approach. However, the data are preliminary, and a large prospective two-arm study is now warranted to compare clinical outcome in (a) patients with positive mid-treatment [^{18}F]FDG-PET findings who continue to receive the installed induction therapy and (b) patients with similar positive [^{18}F]FDG-PET findings in whom treatment is changed to a more aggressive or more experimental one. Other studies will need to investigate the role of a pre-treatment scan and the best timing for the interim scan (after one or after three cycles).

Prognostic value before transplantation

High-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) has been shown to be the best available treatment in patients who have relapsed from lymphoma but who remain chemosensitive [31]. With an intensified preparative regimen in chemosensitive disease, 3-year PFS and OS were improved to 42% and 55%. In chemoresistant disease the PFS and OS were only 22% and 29%, respectively [32]. The IPI at relapse was a significant independent factor for both PFS and OS. During recent years, HDT/ASCT has become a front-line therapy in patients with high–intermediate- or high-risk disease. However, clinical results have been discrepant and additional prognostic factors are needed to predict the final outcome at the time of transplantation. [^{18}F]FDG-PET has become a potential tool to differentiate between responders and non-responders at an earlier time point during chemotherapy than is possible using CT and MRI. However, the predictive value of [^{18}F]FDG-PET with respect to relapse after HDT/ASCT has yet to be established, only a few papers having been published on this issue.

Becherer et al. [33] retrospectively looked at 16 HD/NHL patients at first relapse who all underwent an [^{18}F]FDG-PET scan within 8 weeks prior to HDT/ASCT. The 1-year PFS and OS were 100% for the PET-negative group and only 18% and 55% for the PET-positive group. They concluded that [^{18}F]FDG-PET is accurate in the prediction of relapse prior to HDT/ASCT and that it provides additional information when compared with the IPI. Filmont et al. [34] confirmed these findings and reported a predictive sensitivity and specificity of 92% and 67%, respectively, in 21 HD/NHL patients who underwent [^{18}F]FDG-PET prior to ASCT.

A recent study by Cremerius et al. [35] investigated the predictive value of sequential [^{18}F]FDG-PET before and after front-line HDT/ASCT in 22 NHL patients. Six of the seven patients who did not achieve a partial metabolic response [<25% decrease in standardised uptake value (SUV)] after complete induction therapy developed lymphoma progression, while 10 of the 15 patients with a complete or at least a partial metabolic response remained in complete remission. Median PFS and OS of patients with a less than partial metabolic response after HDT/ASCT were 9 and 29 months, respectively. The strength of [^{18}F]FDG-PET in the study by Cremerius et al. lay in its high positive predictive value for treatment failure in patients who failed to achieve at least a partial response at the end of induction therapy. This was most clearly observed in those patients who were studied after three cycles of induction chemotherapy, thus allowing explicit metabolic response assessment of the late phase of induction therapy. Interestingly, a similar prognostic value was not obtained during the early phase of induction chemotherapy. Moreover, baseline scans before the initiation of treatment as well as the scan after transplantation had no additive prognostic value. The authors also remarked that of the five patients in whom relapse remained undetectable by [^{18}F]FDG-PET at the time of transplantation, three suffered from follicular lymphoma. It seems reasonable to assume that in NHL containing both a high-grade and a low-grade component, [^{18}F]FDG-PET will preferentially assess the therapy response of the high-grade component while the low-grade components may escape detection.

Schot et al. [36] assessed the value of [^{18}F]FDG-PET in relapsed chemosensitive lymphoma patients for the prediction of outcome after HDT/ASCT. Forty-three patients underwent a scan after two courses of induction therapy. PFS was significantly worse for PET-positive patients (6 months) than for PET-negative patients (22 months). They concluded that persistence of [^{18}F]FDG uptake does not necessarily mean an unfavourable outcome, but that the disappearance of abnormal [^{18}F]FDG uptake is correlated with a favourable outcome. These data seem somewhat to contradict the findings of the aforementioned study by Cremerius et al. However, direct comparison is not possible since Cremerius et al. based response assessment on the use of SUVs in sequential PET scans, as suggested by the EORTC functional imaging group in 1999, whereas Schot et al. used a visual scoring system whereby complete disappearance or sustained [^{18}F]FDG uptake was correlated with outcome.

Although [^{18}F]FDG-PET seems to predict outcome in patients treated with HDT/ASCT, these conclusions are still preliminary owing to the small number of patients, the different subtypes of lymphoma studied, the different treatments (first-line vs at relapse), the different timing of the scans and the different criteria used to describe the response (SUV versus visual scores).

Prognostic value in radioimmunotherapy

Radioimmunotherapy (RIT) is a promising approach for the treatment of NHL in patients who have experienced one or more failures of different chemotherapy regimens. The antitumour mechanisms of RIT are highly independent of those of most chemotherapeutic agents and are suited to the treatment of patients who fail primary or salvage chemotherapy. Ultimately, this approach may have a role in the initial treatment of lymphoma patients. Only one full paper has investigated the feasibility of [^{18}F]FDG-PET in monitoring response to RIT. Torizuka et al. [37] investigated 14 low- or intermediate-grade NHL patients and reported that [^{18}F]FDG-PET metabolic data obtained 1–2 months after RIT correlated well with the ultimate best response of NHL to RIT, and more significantly than did the early data after a tracer dose of RIT. Scheidhauer et al. [38] presented in an abstract their data on 22 patients treated with non-myeloablative RIT. They found a rapid decrease in

[18F]FDG uptake as early as 6 weeks after treatment. The decrease in SUV correlated well with clinical outcome. However, four patients had a negative baseline [18F]FDG-PET. Hofmann et al. [39] confirmed these findings in 15 patients.

Before conclusions can be drawn about the prognostic role of [18F]FDG-PET in the therapy monitoring of RIT, more studies with a large number of patients are necessary. The uncertainty about the [18F]FDG avidity of low- and intermediate-grade lymphoma subtypes, the population in which RIT is very promising, is, however, a major limitation.

Shortcomings of [18F]FDG-PET

Specificity

[18F]FDG is not a very tumour-specific substance since anti-inflammatory cells such as activated macrophages, leucocytes or granulation tissue show [18F]FDG avidity. Therefore, active inflammatory lesions (especially after radiotherapy), granulomas and abscesses can be falsely interpreted as malignant residual cells. Moreover, physiological [18F]FDG uptake at the site of thymic hyperplasia, urinary/colonic artefacts and physiological uptake in the muscles could hamper the interpretation of [18F]FDG-PET scans as well as the administration of growth factors. In order to reduce the potentially negative impact of occasional false-positive [18F]FDG-PET results on patient management, it is mandatory to closely correlate the [18F]FDG-PET findings during or after treatment with the pre-treatment scan as well as with the clinical data and the results of other conventional imaging methods.

Sensitivity

A major limitation is the limited spatial resolution of [18F]FDG-PET. For current [18F]FDG-PET instrumentation it is approximately 5–8 mm. Even with the maximal achievable spatial resolution of [18F]FDG-PET (around 2–3 mm), minimal residual disease cannot be excluded and will remain under-diagnosed.

Type of lymphoma

Although [18F]FDG-PET is sensitive in some low- and intermediate-grade lymphomas, the degree of uptake can be lower than that observed in high-grade lymphomas. As most studies concerning therapy monitoring are carried out in patients with high-grade lymphoma, caution should be exercised when interpreting scans of different grades of lymphoma, and extrapolating the results and conclusions to all lymphomas seems to be incorrect.

Limitations of the reported studies

The studies that have been performed are limited by the low patient numbers, variation in the trial populations, relatively short follow-up and their retrospective character. Large prospective trials with consistent patient groups and a long follow-up are necessary in order to avoid the possibility that prejudice will overcome objective evaluation, given that many physicians feel uncomfortable in ignoring positive [18F]FDG-PET findings and feel compelled to change to more aggressive treatment.

Future directions

[18F]FDG-PET has a definite role in therapy monitoring in patients with aggressive NHL and HD. It has become the standard procedure for post-treatment evaluation in routine clinical circumstances, but only large prospective studies will clarify whether [18F]FDG-PET can really replace conventional diagnostic methods in this setting. Promising data are available on the predictive role of [18F]FDG-PET in the context of early therapy monitoring, but larger patient populations and long-term follow-up are necessary to confirm these findings. How such findings will affect therapy management and outcome is an open question at a time when increasing cost-effectiveness has become a hot topic. As current studies are extended, important questions regarding the timing of the interim scan, the role of [18F]FDG-PET in tailoring radiotherapy, its role in low-grade lymphomas, and its value in the context of stem cell transplantation and RIT should be resolved.

An appropriate current strategy for the use of [18F]FDG-PET in the management of lymphoma patients is shown in Fig. 1. We recommend an [18F]FDG-PET scan at diagnosis and after first-line therapy, especially for patients with a residual mass. When abnormal [18F]FDG uptake is present after first-line treatment at initially involved sites without suspicion for inflammation, strong consideration should be given to the use of more aggressive therapy in both NHL and HD patients. A negative [18F]FDG-PET scan does not exclude minimal residual disease and/or late relapse in HD patients with initial stage III or IV disease or in NHL patients. These patients would benefit from repeated follow-up scans for several years. Patients with early stage HD and a negative [18F]FDG-PET scan after therapy are considered to be in complete remission and only need a follow-up [18F]FDG-PET scan if relapse is clinically suspected. Under investigation are the use of an interim [18F]FDG-PET scan during treatment, when a positive scan serves to justify a change to a more aggressive form of therapy, and the performance of an [18F]FDG-PET scan before transplantation or after RIT, when a negative scan is associated with a better long-term outcome.

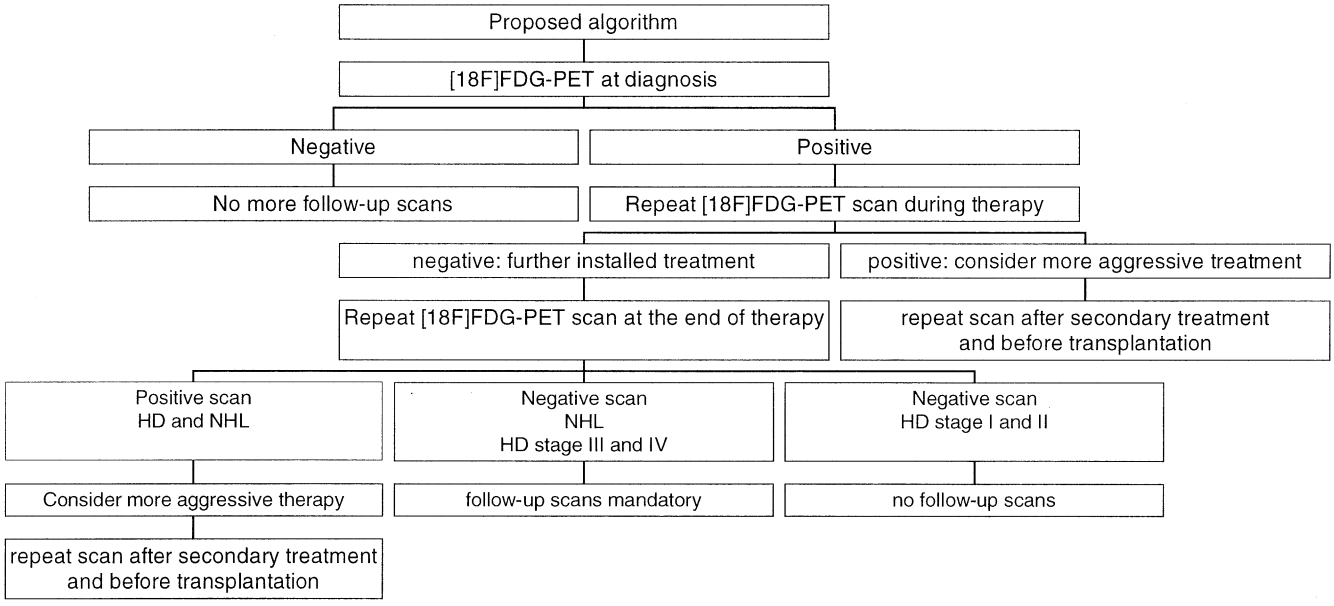

Fig. 1. Implementation of [^{18}F]FDG-PET in the management of lymphoma patients

References

1. Paul R. Comparison of fluorine-18-2-fluorodeoxyglucose and gallium-67 citrate imaging for the detection of lymphoma. *J Nucl Med* 1987; 28:288–292.
2. Kostakoglu L, Goldsmith SJ. Fluorine-18 fluorodeoxyglucose positron emission tomography in the staging and follow-up of lymphoma: is it time to shift gears? *Eur J Nucl Med* 2000; 27:1564–1578.
3. Coiffier B. How to interpret the radiological abnormalities that persist after treatment in non-Hodgkin's lymphoma patients [editorial]? *Ann Oncol* 1999; 10:1141.
4. Russel KJ, Hope RT. Response of mediastinal Hodgkin's disease to radiotherapy: rate of tumor regression not predictive of outcome. *Int J Radiat Oncol Biol Phys* 1989; 16:201–204.
5. Hill M, Cunningham D, MacVicar D, et al. Role of magnetic resonance imaging in predicting relapse in residual masses after treatment of lymphoma. *J Clin Oncol* 1993; 11:2273–2278.
6. Kaplan W, Jochelson MS, Herman TS, et al. Gallium-67 imaging: a predictor of residual tumor viability and clinical outcome in patients with diffuse large-cell lymphoma. *J Clin Oncol* 1990; 8:1966–1970.
7. Janicek M, Kaplan W, Neuberg D, Canellos GP, Shulman LN, Shipp MA. Early restaging gallium scans predict outcome in poor-prognosis patients with aggressive non-Hodgkin's lymphoma treated with high-dose CHOP chemotherapy. *J Clin Oncol* 1997; 15:1631–1637.
8. Front D, Bar-Shalom R, Mor M, et al. Aggressive non-Hodgkin's lymphoma: early prediction of outcome with ^{67}Ga scintigraphy. *Radiology* 2000; 214:253–257.
9. Zinzani PL, Magagnoli M, Chierichetti F, et al. The role of positron emission tomography (PET) in the management of lymphoma patients. *Ann Oncol* 1999; 10:1181–1184.
10. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using F-18-fluorodeoxyglucose for post-treatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has a higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood* 1999; 94:429–433.
11. Maisey NR, Hill ME, Webb A, et al. Are ^{18}fluorodeoxyglucose positron emission tomography and magnetic resonance imaging useful in the prediction of relapse in lymphoma residual masses? *Eur J Cancer* 2000; 36:200–206.
12. Gordon L, Harrington D, Anderson J, et al. Comparison of a second-generation combination chemotherapy regimen (m-BACOP) with a standard regimen (CHOP for advanced diffuse non-Hodgkin's lymphoma. *N Engl J Med* 1992; 327: 1342–1349.
13. Mikhaeel NG, Timothy AR, Odoherty MJ, Hain S, Maisey MN. 18-FDG-PET as a prognostic indicator in the treatment of aggressive non-Hodgkin's lymphoma, comparison with CT. *Leuk Lymphoma* 2000; 39:543–553.
14. Spaepen K, Stroobants S, Dupont P, et al. The prognostic value of positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: ^{18}FDG-PET, a valid alternative to conventional diagnostic methods. *J Clin Oncol* 2000; 19:414–419.
15. Juweid ME, Wiseman GA, Menda Y, Vose J, Links B, Graham MM. FDG-PET in the prediction of progression free survival at 1-year of patients with aggressive non-Hodgkin's lymphoma following antracycline based first line chemotherapy [abstract]. *Eur J Nucl Med* 2002; 29 (Suppl 1):S264.
16. Aisenberg AC. Problems in Hodgkin's disease management. *Blood* 1999; 93:761–779.
17. de Wit M, Bohuslavizki KH, Buchert R, Bumann D, Clausen M, Hossfeld DK. ^{18}FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's disease. *Ann Oncol* 2001; 12:29–37.
18. Weihrauch MR, Re D, Scheidhauer K et al. Thoracic positron emission tomography using ^{18}F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 2001; 98:2930–2943.
19. Spaepen K, Stroobants S, Dupont P et al. Can positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG-PET) after first line treatment distinguish Hodgkin's disease patients who need additional therapy from others where additional

therapy would mean avoidable toxicity? *Br J Haematol* 2001; 115:272–278.
20. Mikhaeel NG, Mainwaring P, Nunan T, Timothy AR. Prognostic value of interim and post treatment FDG-PET scanning in Hodgkin lymphoma [abstract]. *Ann Oncol* 2002; 13 (Suppl 2):21.
21. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; 329:987–994.
22. Armitage J, Weisenburger D, Hutchins M, et al. Chemotherapy for diffuse large-cell lymphoma—rapidly responding patients have more durable remissions. *J Clin Oncol* 1986; 4:160–164.
23. Thomas F, Cosset J-M, Cherel P, et al. Thoracic CT-scanning follow-up of residual mediastinal masses after treatment of Hodgkin's disease. *Radiother Oncol* 1988; 11:119–122.
24. Hoekstra OS, van lingen A, Ossenkoppele GJ, et al. Early response monitoring in malignant lymphoma using fluorine-18-fluorodeoxyglucose single-photon emission tomography. *Eur J Nucl Med* 1993; 20:1214–1220.
25. Dimitrakopoulou-Strauss A, Strauss LG, Goldschmidt H, et al. Evaluation of tumor metabolism and multidrug resistance in patients with treated malignant lymphomas. *Eur J Nucl Med* 1995; 22:434–442.
26. Römer W, Hanauske AR, Ziegler S, et al. Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. *Blood* 1998; 91:4464–4471.
27. Jerusalem G, Beguin Y, Fassotte M-F, et al. Persistent tumor^{18}F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. *Haematologica* 2000; 85:613–618.
28. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with ^{18}F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. *Ann Oncol* 2002; 13:1356–1363.
29. Kostakoglu L, Coleman M, Leonard JP, Kuji I, Zoe H, Goldsmith SJ. PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma ad Hodgkin's disease. *J Nucl Med* 2002; 43:1018–1027.
30. Lowe VJ, Wiseman GA. Assessment of lymphoma therapy using^{18}F-FDG-PET. *J Nucl Med* 2002; 43:1028–1030.
31. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemosensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; 333:1540–1545.
32. Stiff PJ, Dahlberg S, Forman SJ, et al. Autologous bone marrow transplantation for patients with relapses or refractory diffuse aggressive non-Hodgkin's lymphoma: value of augmented preparative regimes. *J Clin Oncol* 1998; 16:48–55.
33. Becherer A, Mitterbauer M, Jaeger U, et al. Positron emission tomography with FDG-PET predicts relapse of malignant lymphoma after high-dose therapy with stem cell transplantation. *Leukemia* 2002; 16:260–267.
34. Filmont JE, Yap C, Emmanouilides C, et al. Prognostic value^{18}F-FDG-PET after high-dose chemotherapy and prior to autologous stem cell transplantation in lymphoma [abstract]. *J Nucl Med* 2002; 43 (Suppl): 78P.
35. Cremerius U, Fabry U, Wildberger JE, et al. Pre-transplant positron emission tomography using fluorine-18-fluoro-deoxyglucose predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2002; 30:103–111.
36. Schot BW, Pruim J, van Imhoff GW, Sluiter W, Vellenga E, Vaalburg W. Early FDG-PET for the prediction of long-term outcome in chemo-sensitive relapsed lymphoma [abstract]. *Eur J Nucl Med* 2002; 29 (Suppl 1):S113.
37. Torizuka T, Zasadny KR, Kison PV, Rommelfanger SG, Kaminski MS, Wahl RL. Metobolic response on non-Hodgkin's lymphoma to^{131}I-anti-B1 radioimmunotherapy: evaluation with FDG-PET. *J Nucl Med* 2000; 41:999–1005.
38. Scheidhauer K, Wolf I, von Schilling C, et al. Outcome prediction of radioimmunotherapy of NHL by FDG-PET [abstract]. *Eur J Nucl Med* 2002; 29 (Suppl 1):S113.
39. Hofmann M, Hertenstein B, Boerner AR, et al. 18-F-FDG PET in monitoring therapy response to RIT by 131-I rituximab antibody [abstract]. *Ann Oncol* 2002; 13 (Suppl 2):96.