ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Evaluation of Therapy for Lymphoma

Guy Jerusalem, MD, PhD,* Roland Hustinx, MD, PhD,† Yves Beguin, MD, PhD,* and Georges Fillet, MD, PhD*

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the best noninvasive imaging technique for to assess response in patients suffering from lymphoma. Early response evaluation ("interim PET") after one, a few cycles, or at midtreatment can predict response, progression-free survival, and overall survival. We calculated from data of 7 studies an overall sensitivity to predict treatment failure of 79%, a specificity of 92%, a positive predictive value (PPV) of 90%, a negative predictive value (NPV) of 81%, and an accuracy of 85%. Although it is not yet indicated to change patient management based on residual ^{18}F-FDG uptake on interim scan in chemotherapy-sensitive patients, prospective studies evaluating the role of an interim PET in patient management clearly are warranted. ^{18}F-FDG PET also has an important prognostic role in relapsing patients after reinduction chemotherapy before high-dose chemotherapy (HCT) followed by autologous stem cell transplantation (ASCT). However, all chemotherapy-sensitive patients remain candidates for HCT followed by ASCT, even if ^{18}F-FDG PET showed residual ^{18}F-FDG uptake. We calculated from data of 3 studies an overestimated risk of relapse in 16% of all PET-positive patients. Some patients with residual ^{18}F-FDG uptake will have a good outcome after HCT followed by ASCT. ^{18}F-FDG PET is the imaging technique of choice for end-of-treatment evaluation. However, ^{18}F-FDG is not specific for tumoral tissue. Active inflammatory lesions and infectious processes can be falsely interpreted as malignant residual cells. However, a negative ^{18}F-FDG PET cannot exclude minimal residual disease. Consequently, it is always indicated to correlate PET findings with clinical data, other imaging modalities, and/or a biopsy. We calculated, from data of 17 studies in end-of-treatment evaluation, a sensitivity of 76%, a specificity of 94%, a PPV of 82%, a NPV 92%, and an accuracy of 89%.
Semin Nucl Med 35:186-196

Patients suffering from Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) can be cured by appropriate radiotherapy and/or chemotherapy. Long-term survival rates are as high as 90% for subgroups of patients with HD and 50% for those with high-grade NHL. Relapsing patients can be cured by second-line salvage treatments, including most times high-dose chemotherapy (HCT) followed by autologous stem cell transplantation (ASCT). Accurate staging and restaging allows the optimal selection of treatment options. Shorter treatment cycles are the goal of ongoing research in a subgroup of low-risk patients in an attempt to minimize side effects related to treatment. High-risk patients or those with persisting disease after first-line therapy may benefit from more aggressive treatments. The assessment of response to treatment is one of the most challenging aspects in the imaging of patients suffering from lymphoma. It is reasonable to use salvage therapy at the time of minimal residual disease rather than at the time of a clinically overt relapse. Furthermore, the earlier discontinuation of an unsuccessful treatment would avoid the associated toxicity. The presence of a residual mass during or after treatment is an important clinical issue. Unfortunately, computed tomography (CT) and magnetic resonance imaging (MRI) are unable to differentiate residual disease from fibrosis.

Until recently, gallium-67 (^{67}Ga) scintigraphy was the imaging technique of choice to assess response to treatment in HD and in high-grade NHL. However, it suffers from low spatial resolution and a lack of specificity. Its sensitivity is low in infradiaphragmatic disease because of physiological uptake in the abdomen. Its limitations in low-grade NHL also are well known. Moreover, a ^{67}Ga scintigraphy should always be performed before treatment to determine whether the individual patient has a gallium-avid lymphoma.[1] Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose

*Division of Medical Oncology, Department of Medicine, University of Liège, Liège, Belgium.
†Division of Nuclear Medicine, Department of Medicine, University of Liège, Liège, Belgium.
Address reprint requests to Guy Jerusalem, MD, PhD, Medical Oncology, CHU Sart Tilman, B35, B-4000 - Liege 1, Belgium. E-mail: g.jerusalem@chu.ulg.ac.be

 0001-2998/05/$-see front matter
doi:10.1053/j.semnuclmed.2005.02.004

(^{18}F-FDG) is now widely used in the management of malignant tumors including lymphoma.[2] Despite the important role of ^{67}Ga scintigraphy in response evaluation, it appears now that ^{18}F-FDG PET is more sensitive for the detection of nodal and extranodal sites of disease.[3-10] Furthermore, ^{18}F-FDG PET also is considered to be more convenient than ^{67}Ga scintigraphy because a PET study can be performed 1 hour after the injection of ^{18}F-FDG whereas the scintigraphy must be performed several days after the administration of ^{67}Ga. ^{18}F-FDG PET is without any doubt the best noninvasive imaging technique for response assessment in patients suffering from lymphoma.

Consequently, it is very important to take into account the shortcomings of ^{18}F-FDG PET to avoid misinterpretation of PET findings. Current ^{18}F-FDG PET instrumentations have a spatial resolution of approximately 5 to 8 mm. Radiotracer uptake in structures less than twice the spatial resolution of the tomograph can be underestimated (= partial volume effect). There is also a risk of temporarily reduced metabolic activity after chemotherapy. Early assessment of response is performed, whenever possible, the last day before or even the same day of a new cycle of chemotherapy. The best time for end of treatment evaluation remains unknown, but most investigators suggest waiting at least 1 month after the last day of chemotherapy and 3 months after the last dose of radiotherapy. It is important to understand that ^{18}F-FDG PET can never exclude minimal residual disease, even if the spatial resolution of ^{18}F-FDG PET improves in the future.[11] It is not possible to decide to stop a treatment based only on a negative ^{18}F-FDG PET. It may be indicated to repeat ^{18}F-FDG PET during routine follow-up to overcome insecurities regarding the potential of residual tumor at the end of treatment.[12] Residual lymphoma also may be missed or its extent underestimated because the lymphoma is not ^{18}F-FDG avid or has very low-grade uptake, but this is extremely uncommon.[13-17] However, positive findings on PET do not necessarily represent residual disease. Meticulous evaluation of PET images is mandatory to avoid false-positive PET findings associated with muscular tension or normal intestinal structures. Brown fat can avidly incorporate ^{18}F-FDG, especially in lean patients.[18] Physiological uptake can be misinterpreted, particularly by an inexperienced observer. ^{18}F-FDG is not a tumor-specific radiotracer because antiinflammatory cells, such as activated macrophages, leukocytes or granulation tissues, show ^{18}F-FDG avidity. Therefore, active inflammatory lesions and infectious processes can be falsely interpreted as malignant residual cells. Documented causes of false-positive PET studies in response assessment of lymphoma patients are shown in Table 1.[19-43] A nuclear medicine physician experienced in ^{18}F-FDG PET interpretation often will be able to recognize patterns of uptake as being caused by benign processes. He or she also will be able to recognize when benign cannot be differentiated from malignant and, consequently, whether further workup is indicated.

Table 1 Documented Causes of False-Positive ^{18}F-FDG PET Studies in Response Evaluation (Adapted from Jerusalem and Hustinx[19])

Second primary[20-22]
Thyroid adenoma[23]
Rebound thymic hyperplasia[23-28]
Infectious process[26]
Toxoplasmosis[29]
Tuberculosis[22]
Pneumonia[30]
Radiotherapy induced pneumonia[31,32]
Inflammatory lung process[23]
Pleural inflammation[33]
Histiocytic reaction[25,34]
Benign follicular lymph node hyperplasia[22,35]
Unspecific lymphadenitis[36]
Granulomatous lymphadenitis[26]
Sarcoidosis and sarcoid-like reaction[37]
Epitheloid cell granuloma[38]
Eosinophilic granuloma[39]
Erythema nodosum[40]
Fracture at the site of lymphoma infiltration before treatment[30]
Fistula[41]
Granulation tissue[42]
Non-viable scar tissue[43]

Early Response Evaluation

Early prediction of response to therapy could potentially identify those patients who will benefit most from standard conventional therapy and those for whom alternative treatment strategies might prove more effective. Previous studies have suggested that patients with a rapid response to induction treatment based on conventional imaging techniques are more likely to have a better and more durable response.[44-46] However, tumor volume reduction based on radiological criteria is a late sign of effective therapy, and an accurate definition of complete remission is difficult when residual masses are observed. However, time to reach complete remission based on radiological criteria is an imperfect indicator of the quality of response because the degree of tumor reduction differs between patients according to the size of initial masses, their site, histology, and the type of treatment.[47] Functional imaging techniques, such as ^{67}Ga scintigraphy, are very useful in the monitoring of response to treatment. ^{67}Ga scintigraphy after 1 cycle,[48] 2 cycles,[49] 2 to 5 cycles,[48] or 4 to 6 cycles[50,51] reliably predicts outcome in patients with lymphoma.

However, Friedberg and coworkers[7] showed that persistently positive ^{18}F-FDG PET scans after 3 cycles of chemotherapy have a higher sensitivity for the prediction of a subsequent relapse compared with ^{67}Ga scintigraphy. Zijlstra and coworkers[20] also found better test characteristics (better positive predictive value, negative predictive value, and interobserver agreement) for ^{18}F-FDG PET compared with ^{67}Ga scintigraphy in response evaluation after 2 cycles of polychemotherapy. A rapid decrease of ^{18}F-FDG uptake by tumoral tissue has been observed as early as 7 days after the first administration of chemotherapy in patients with NHL.[52] The best timing for early response as-

Table 2 Predictive Value of Whole-Body ^{18}F-FDG PET for Early Response Assessment (Adapted from Jerusalem and Hustinx[19])

Authors	No. of Cycles Before Evaluation	Median Follow-Up (Months)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Mikhaeel et al[53]	2-4	30	100% (7/7)	94% (15/16)	87% (7/8)	100% (15/15)	96% (22/23)
Jerusalem et al[54]	3 (2-5)	17	42% (5/12)	100% (14/14)	100% (5/5)	67% (14/21)	73% (19/26)
Kostakoglu et al[55]	1	19	87% (13/15)	87% (13/15)	87% (13/15)	87% (13/15)	87% (26/30)
Spaepen et al[56]	3-4	36	85% (33/39)	100% (31/31)	100% (33/33)	84% (31/37)	91% (64/70)
Zijlstra et al[20]	2	25	64% (9/14)	75% (9/12)	75% (9/12)	64% (9/14)	69% (18/26)
Torizuka et al[57]	1-2	24	87% (14/16)	50% (2/4)	87% (14/16)	50% (2/4)	80% (16/20)
Friedberg et al[7]	3	24	80% (4/5)	94% (16/17)	80% (4/5)	94% (16/17)	91% (20/22)
Overall			79% (85/108)	92% (100/109)	90% (85/94)	81% (100/123)	85% (185/217)

sessment remains unknown. Early response evaluation by ^{18}F-FDG PET ("interim PET") after one, a few cycles, or at midtreatment can predict response, progression-free survival (PFS), and overall survival (OS) in lymphoma patients (Table 2).[7,20,53-57] Most studies included only patients suffering from NHL,[20,53,54,56] 2 studies included a mixed patient population,[55,57] and 1 study included only patients suffering from HD.[7] Results in HD are very preliminary because 181 of the 217 patients included in these 7 studies suffered from NHL. In one study,[55] a dual-head coincidence camera was used, whereas the others used dedicated PET systems. We calculate for PET an overall sensitivity of 79%, a specificity of 92%, a positive predictive value (PPV) of 90%, a negative predictive value (NPV) of 81%, and an accuracy of 85% (Table 2).

Spaepen and coworkers[56] showed that the predictive value of ^{18}F-FDG PET is independent of conventional prognostic factors before treatment (International Prognostic Index: IPI). Kostakoglu and coworkers[55] reported that PET findings obtained after the first cycle correlated better with PFS than ^{18}F-FDG PET findings obtained after completion of chemotherapy. Most studies are oversimplified by defining only 2 categories of patients, either with or without residual ^{18}F-FDG uptake in areas initially involved by lymphoma. Mikhaeel and coworkers[53] described a third group of patients with minimal residual uptake on interim PET defined as low-grade, just above the background, in only one focus. The authors analyzed these patients together with PET-negative patients because they observed no relapse in all 4 patients presenting minimal residual uptake. Semiquantitative studies may be more appropriate but methodological problems remain to be resolved.[58] A rapid decrease of tumor size may influence ^{18}F-FDG uptake. Residual radioactivity concentration in structures less than twice the spatial resolution of the tomograph can be underestimated (partial volume effect). The use of SUV analysis also must take into account the influence of different imaging times over multiple bed positions because ^{18}F-FDG uptake in lymphoma does not reach a plateau in the 3-hour postinjection time.

^{18}F-FDG PET is the best noninvasive imaging technique for early response evaluation (Figs. 1-3). At this time it allows one to separate 2 categories of patients, either with or without residual ^{18}F-FDG uptake. However, ^{18}F-FDG PET is not a perfect indicator of response because some PET-positive patients will have a good outcome (Fig. 4). The probability that PET remains positive depends on the sensitivity of the tomograph (smallest lesion that can be detected), the biology of the tumor (more rapid response in aggressive tumors), the tumor mass at diagnosis (tumor shrinkage below the detection level, later in larger tumors), the drugs used (impact of monoclonal antibodies such as rituximab), the dose-intensity of chemotherapy (more rapid regression if higher doses), and the interval between the last day of chemotherapy and ^{18}F-FDG PET (risk of temporarily reduced metabolic activity early after chemotherapy). Furthermore, Spaepen and coworkers[59]

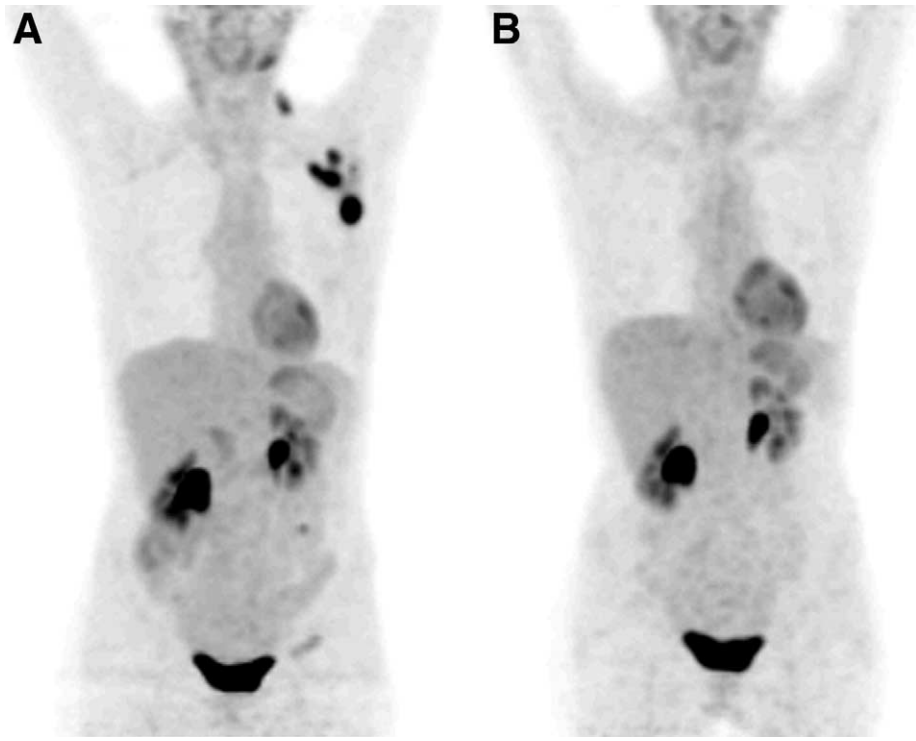

Figure 1 Stage IIA high-grade NHL in a 53-year-old patient. ^{18}F-FDG PET performed at diagnosis shows highly hypermetabolic lymph nodes in the left axillary and cervical areas (A, 3D projection image). PET performed after 3 courses of chemotherapy shows a complete metabolic response (B, 3D projection image). The patient is in complete clinical remission 6 months after completing the treatment.

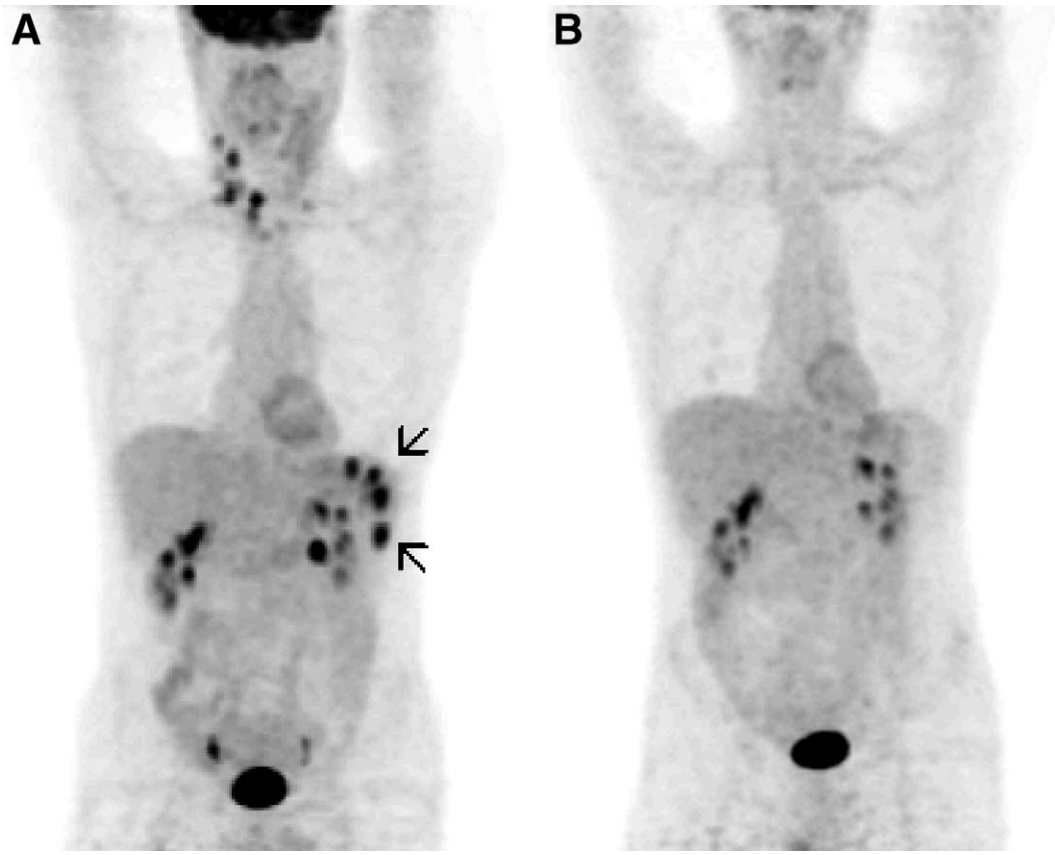

Figure 2 Diffuse large B-cell NHL in a 49-year-old patient. ^{18}F-FDG PET performed at baseline shows several foci of increased activity in the right cervical and infraclavicular areas, as well as in the spleen (arrows in A, 3D projection image). ^{18}F-FDG PET performed after completion of induction chemotherapy (4 courses) shows a normal distribution of the tracer (B, 3D projection image). No relapse was observed (follow-up: 1 year).

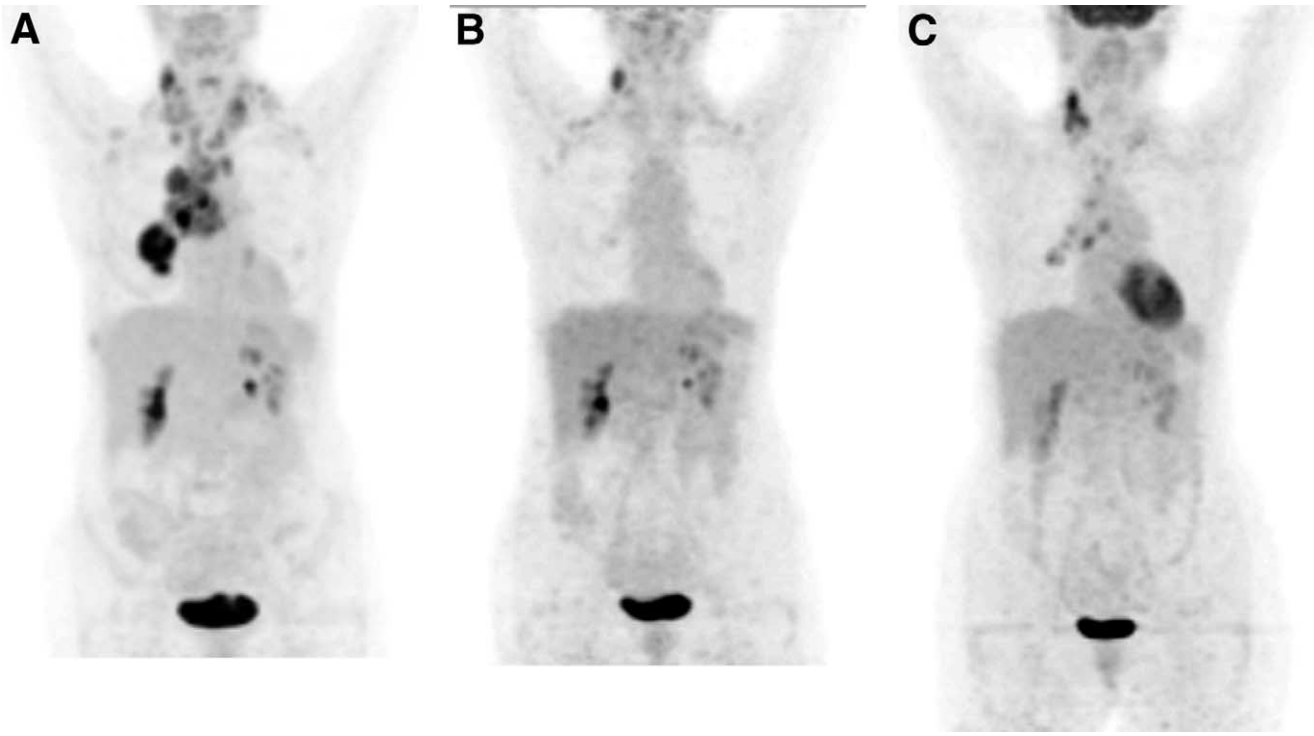

Figure 3 HD in a 56-year-old woman. ^{18}F-FDG PET performed at baseline shows multiple foci of increased activity in cervical and mediastinal areas as well as right hilar and lung infiltration (A, 3D projection image). ^{18}F-FDG PET performed after 2 cycles of polychemotherapy indicates residual ^{18}F-FDG uptake in a right cervical lymph node (B, 3D projection image). Treatment failure was observed at the end of treatment (C, 3D projection image).

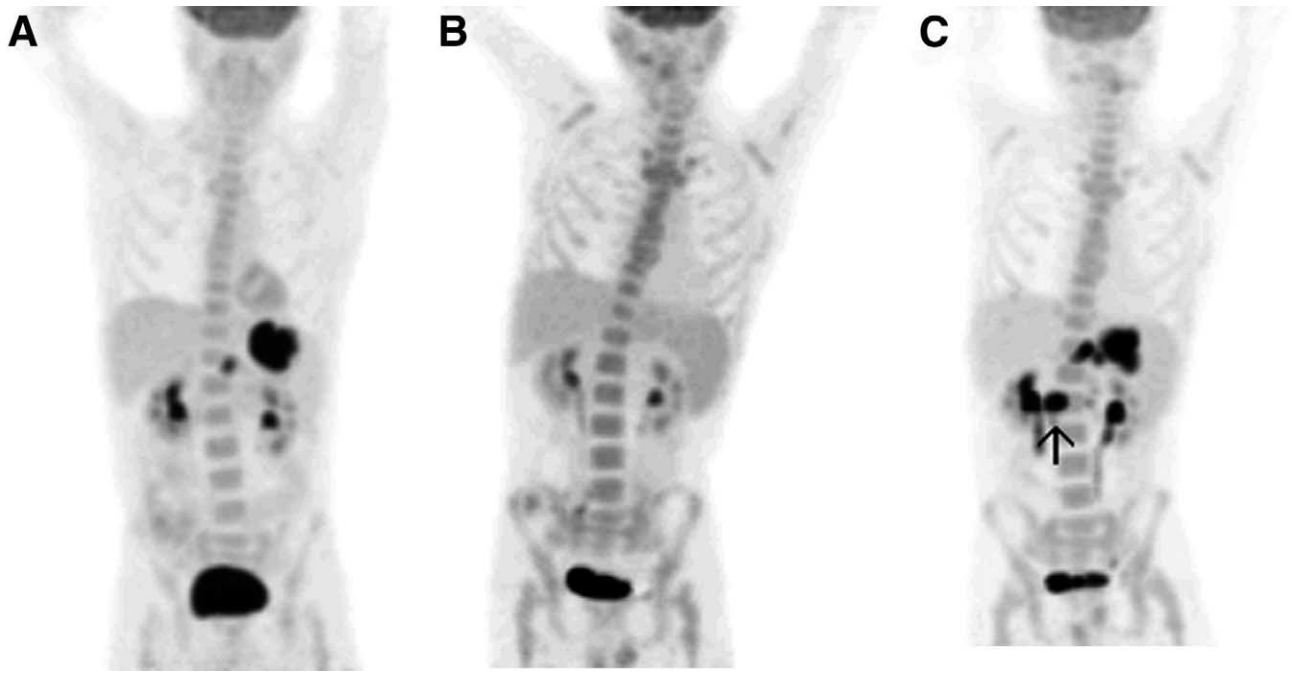

Figure 4 High-grade gastric NHL in a 42-year-old man. In addition to the large gastric mass, ^{18}F-FDG PET also shows increased activity in a celiac node (A, 3D projection image). Even though the PET study performed 5 weeks later, early on during treatment, showed complete remission (B, 3D projection image), a locoregional recurrence was observed 6 months later, as well as right para-aortic nodes (arrow in C, 3D projection image).

Table 3 Predictive Value of Whole-Body ^{18}F-FDG PET After Reinduction Chemotherapy Before Autologous Stem Cell Transplantation

Authors	Median Follow-Up (Months)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Becherer et al[41]	13	100% (8/8)	71% (5/7)	80% (8/10)	100% (5/5)	87% (13/15)
Cremerius et al[63]	30	58% (7/12)	83% (10/12)	78% (7/9)	67% (10/15)	71% (17/24)
Spaepen et al[62]	50	90% (26/29)	86% (25/29)	87% (26/30)	89% (25/28)	88% (51/58)
Overall		84% (41/49)	83% (40/48)	84% (41/49)	83% (40/48)	84% (81/97)

have shown in a tumor mouse model that a transient increase in inflammatory cells may result in overestimation of the fraction of viable cancer cells. Consequently, it is not yet indicated to change patient management based on residual ^{18}F-FDG uptake on interim scan in chemotherapy-sensitive patients. However, prospective studies evaluating the role of interim PET in patient management are clearly warranted.

Evaluation of Chemosensitivity Before High-Dose Chemotherapy

HCT followed by ASCT is the treatment of choice for patients who relapse from NHL after conventional chemotherapy but who remain chemotherapy-sensitive.[60] It is also the best treatment option for most patients who suffer from relapsing or progressive HD after standard treatment.[61] ^{18}F-FDG PET may be able to better predict which chemosensitive patients might ultimately benefit from ASCT. Unfortunately, conventional diagnostic methods are not very accurate for the selection of patients who would benefit from ASCT. In fact, half of chemotherapy-sensitive patients suffering from NHL will relapse after ASCT, resulting in an overall survival in relapsed patients of only 25% to 30% at 2 years.[60] Table 3 summarizes the results of 3 recent studies evaluating the role of ^{18}F-FDG PET after induction chemotherapy. We excluded from analysis all 3 patients with treatment-related mortality. These 3 studies, including either mostly[41,62] or exclusively[63] NHL patients, showed that ^{18}F-FDG PET used after induction chemotherapy is now the imaging technique of choice to predict outcome after ASCT. False-negative ^{18}F-FDG PET studies have been reported, in particular in follicular lymphoma of grade 1 or with secondary transformation to grade 3.[63]

One can argue that the early identification of treatment failure has only minimal therapeutic consequences because HCT followed by ASCT is indicated in every case, as it is the only available therapeutic option. However, new therapeutic concepts, such as nonmyeloablative allogenic transplants, are emerging. ^{18}F-FDG PET may allow a better identification of candidates for more innovative approaches. However, ^{18}F-FDG PET is not a perfect indicator of outcome. The PPV, NPV, and accuracy calculated from the 3 studies summarized in Table 3 are, respectively, 84%, 83%, and 84%. Consequently, not all patients with a negative PET have a favorable outcome and not all patients with a positive PET will relapse. Patients with a negative PET after the reinduction chemotherapy have a better prognosis and are good candidates for HCT followed by ASCT. However, it is not indicated to exclude chemotherapy-sensitive PET-positive patients from ASCT based on an overestimated risk of relapse in 16% of all PET-positive patients. Some patients with residual ^{18}F-FDG uptake will have a good outcome after HCT followed by ASCT. ^{18}F-FDG PET provides additional informations when compared with the IPI[63] or with the age-adjusted IPI.[41]

Spaepen and coworkers[62] reported that ^{18}F-FDG PET before transplantation is even a stronger prognostic factor than IPI. The standard uptake values (SUVs) in patients with a later relapse are higher than in patients remaining in clinical complete remission.[41] There is also only a significant decrease of SUV after induction chemotherapy in patients who reached a clinical complete remission after ASCT.[41] However, semiquantitative sequential studies add no useful prognostic information compared with a single ^{18}F-FDG PET study (even without semiquantitative analysis) realized at the end of treatment. Cremerius and coworkers[63] suggested that sequential ^{18}F-FDG PET after 3 cycles and before HCT is indicated for response evaluation in patients undergoing 5 to 7 courses of induction chemotherapy. However, when the analysis was restricted to ^{18}F-FDG PET findings after induction chemotherapy and before HCT, similar results were obtained: 5 of 15 patients with a negative PET relapsed compared with 7 of 9 patients with a positive PET (data included in Table 3). Unfortunately, this easier and less-expensive approach was not discussed by the authors.

The prognostic value of ^{18}F-FDG PET is higher at the end of induction chemotherapy than after transplantation.[63] The sensitivity and NPV is lower after transplantation probably because of a transient reduction of tumoral glucose metabolism shortly after intense therapy. Interestingly, a similar prognostic value also was not obtained during the early phase of induction therapy. Cremerius and coworkers[63] showed that only a sustained response to induction therapy is predictive of more favorable outcome. In contrast, sequential PET studies at baseline and after 3 of 5 to 7 cycles of induction therapy were not able to predict outcome. The results reported by Schot and coworkers[64] in early response evaluation after 2 cycles of reinduction chemotherapy also are rather disappointing. If the analysis is restricted to patients who really undergo ASCT, they observed a sensitivity of 72% (13/18), a spec-

Table 4 Predictive Value of Whole-Body ^{18}F-FDG PET for Post-Treatment Evaluation in a Mixed Patient Population (Adapted from Jerusalem and Hustinx[19])

Authors	Median Follow-Up (Months)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
de Wit et al[30]	14	100% (12/12)	77% (17/22)	70% (12/17)	100% (17/17)	85% (29/34)
Jerusalem et al[11]	23	43% (6/14)	100% (40/40)	100% (6/6)	83% (40/48)	85% (46/54)
Zinzani et al[75]	20	93% (13/14)	100% (30/30)	100% (13/13)	97% (30/31)	98% (43/44)
Bangerter et al[24]	31	71% (5/7)	86% (25/29)	56% (5/9)	93% (25/27)	83% (30/36)
Mikhaeel et al[76]	38	80% (8/10)	95% (21/22)	89% (8/9)	91% (21/23)	91% (29/32)
Naumann et al[43]	35	71% (5/7)	94% (48/51)	62% (5/8)	96% (48/50)	91% (53/58)
Zinzani et al[35]	12	100% (14/14)	97% (59/61)	87% (14/16)	100% (59/59)	97% (73/75)
Foo et al[77]	26	57% (4/7)	100% (17/17)	100% (4/4)	85% (17/20)	87% (21/24)
Overall		79% (67/85)	94% (257/272)	82% (67/82)	93% (257/275)	91% (324/357)

ificity of 48% (10/21), a PPV of 54% (13/24), a NPV of 67% (10/15), and an accuracy of 59% (23/39). The accuracy is improved to 65% if the 7 patients who were not transplanted are included in the analysis. Finally, Filmont and coworkers[65] reported more encouraging results. They observed that ^{18}F-FDG PET performed 2 to 5 weeks after the initiation of salvage chemotherapy can be used to predict outcome of patients suffering from lymphoma with high accuracy. Seven of 8 patients with a negative PET remained in complete remission, and 11 of 12 patients with a positive ^{18}F-FDG PET relapsed after ASCT.

In our opinion, at this time, ^{18}F-FDG PET has only an important prognostic role in the pretransplantation evaluation of patients with lymphoma. It is not yet indicated to change the management of chemotherapy-sensitive patients based on ^{18}F-FDG PET. All chemotherapy-sensitive patients are candidates for HCT followed by ASCT, even if the ^{18}F-FDG PET scan remains positive after induction chemotherapy. An important challenge for the future is the development of successful treatment strategies for chemotherapy-refractory patients. These patients may benefit from more experimental treatment options in an ultimate attempt to overcome the poor clinical outcome.

Evaluation After Completion of Chemotherapy and/or Radiotherapy

Achieving a complete remission is a major objective in patients with HD or NHL because it usually is associated with a longer progression-free survival than a partial remission.[66] However, in as many as 64% of all HD cases[67,68] and in 30% to 60% of all NHL cases,[69] computed tomography or magnetic resonance imaging show abnormalities during restaging. Residual masses are observed more frequently in patients with an aggressive NHL and a large tumor mass at diagnosis and in patients suffering from scleronodular HD. Unfortunately, conventional imaging cannot differentiate between benign fibrous tissue, an inflammatory process, or persistent malignant disease. Only a maximum of 20% of residual masses at the completion of treatment are reported to be positive for lymphoma on biopsy and will eventually relapse.[70-74] If the tumor is easily accessible, such as an enlarged peripheral lymph node, the questionable lesion should be excised and histologically analyzed. In other localizations, it is much more difficult to perform the biopsy. For example, a mediastinal tumor can only be biopsied by mediastinoscopy or open thoracic surgery. This procedure is associated with some morbidity and a high failure rate for a pathological diagnosis because of the relative small amount of tissue that can be resected.

Therefore, functional imaging techniques are of great interest in this situation. ^{67}Ga scintigraphy has become a standard procedure to assess remission and the nature of residual masses.[71] However, its sensitivity for staging lymphoma varies with the localization, the size, and the cell type of the lesion. Recent studies indicate the high accuracy of ^{18}F-FDG PET for end-of-treatment response assessment.[7,11,24-26,30,33,35,36,53,75-80] Two studies compare directly ^{18}F-FDG PET and ^{67}Ga scintigraphy.[7,77] Friedberg and coworkers[7] found a sensitivity of 80% for ^{18}F-FDG PET compared with 40% for ^{67}Ga scintigraphy. Foo and coworkers[77] observed that ^{18}F-FDG PET has superior accuracy in staging and restaging compared with gallium scans. The PPV of PET and gallium scans for relapse given a residual mass were 100% and 0%, respectively. The NPV was 76% and 70%, respectively. ^{18}F-FDG PET is now considered the noninvasive imaging technique of choice for the detection of residual disease after treatment. According to the clinical situation, it allows either directed biopsies to be performed or further treatment to be administered. A positive ^{18}F-FDG PET study after treatment is related in most patients to residual tumor cells accumulating the radiotracer.

However, ^{18}F-FDG uptake is not specific for tumoral tissue. In particular, when abnormal ^{18}F-FDG uptake is observed outside the initially involved sites, infectious or inflammatory lesions have to be excluded. Consequently, it is always indicated to correlate PET findings with clinical data, other imaging modalities, and/or a biopsy before starting salvage therapy. However, a negative ^{18}F-FDG PET study cannot exclude minimal residual disease leading later to a clini-

Table 5 Predictive Value of Whole-Body ^{18}F-FDG PET for Post-Treatment Evaluation in HD (Adapted from Jerusalem et al[19,87])

Authors	Median Follow-Up (Months)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
de Wit et al[33]	26	100% (10/10)	78% (18/23)	67% (10/15)	100% (18/18)	85% (28/33)
Dittmann et al[36]	6	87% (7/8)	94% (17/18)	87% (7/8)	94% (17/18)	92% (24/26)
Spaepen et al[78]	32	50% (5/10)	100% (50/50)	100% (5/5)	91% (50/55)	92% (55/60)
Weihrauch et al[25]	28	67% (6/9)	80% (16/20)	60% (6/10)	84% (16/19)	76% (22/29)
Guay et al[79]	16	79% (11/14)	97% (33/34)	92% (11/12)	92% (33/36)	92% (44/48)
Friedberg et al[7]	24	80% (4/5)	85% (23/27)	50% (4/8)	96% (23/24)	84% (27/32)
Panizo et al[26]	28	100% (9/9)	85% (17/20)	75% (9/12)	100% (17/17)	90% (26/29)
Overall		80% (52/65)	91% (174/192)	74% (52/70)	93% (174/187)	88% (226/257)

cal relapse. Tables 4 through 6 summarize the predictive value of whole-body PET in the end of treatment evaluation as reported in selected papers written in English. We are aware of the limitations of these studies. Patient populations were small and most times very heterogenous. The natural history of low-grade and high-grade NHL is very different, but all patients were analyzed together in some studies. The follow-up time also is a critical factor. However, these studies give us useful informations about the value of ^{18}F-FDG PET in the end of treatment evaluation. In a mixed population of 357 patients (HD: 174, NHL: 183[11,24,30,35,43,75-77] we calculated an overall sensitivity of 79%, a specificity of 94%, a PPV of 82%, a NPV of 93%, and an accuracy of 91%. Three articles[31,81,82] were not included because only the region of interest (residual mass) instead of the whole-body was studied by ^{18}F-FDG PET in most patients.

Lavely and coworkers[83] reported only PET findings in the areas initially involved by lymphoma. Furthermore, 12 of 40 patients received radiotherapy after ^{18}F-FDG PET, potentially influencing outcome, explaining why this study was not included in Table 4. In a selected group of 257 patients suffering from HD (Table 5),[7,25,26,33,36,78,79] we calculated a sensitivity of 80%, a specificity of 91%, a PPV of 74%, a NPV of 93%, and an accuracy of 88%. Two articles[23,84] were not included because some patients underwent ^{18}F-FDG PET several times. Two studies included only patients with NHL (Table 6).[53,80] We calculated a sensitivity of 67%, a specificity of 100%, a PPV of 100%, a NPV of 83%, and an accuracy of 88% for this group of patients. Finally, we found for all patients included in Table 4 to 6 a sensitivity of 76% (154/202), a specificity of 94% (517/550), a PPV of 82% (154/187), a NPV of 92% (517/565), and an accuracy of 89% (671/752). In an update of our results presented at the ASCO meeting in 2003,[21] we found a sensitivity of 33% (1/3), a specificity of 94% (34/36), a PPV of 33% (1/3), a NPV of 94% (34/36), and an accuracy of 90% (35/39) in HD. We observed a sensitivity of 48% (11/23), a specificity of 96% (44/46), a PPV of 85% (11/13), a NPV of 79% (44/56), and an accuracy of 80% (55/69) in NHL.

We explain the differences observed in our experience and in the literature according to histologic subtypes by the better prognosis in HD. Because a relapse is a rare event in HD, the impact of a false-positive PET on the PPV is more important in HD than in NHL. However, the NPV is lower in NHL than in HD. In fact, the risk of relapse is more important in patients with NHL, and PET cannot exclude minimal residual disease. The predictive value of relapse depends not only on histologic subtype but also on the initial prognostic factors. The PPV will be higher and the NPV will be lower in a study population including more high-risk patients. Cremerius and coworkers[85] observed a NPV of 90% in moderate-risk patients compared with 50% to 67% in high-risk patients. Patient selection criteria also have an impact on the results. Inclusion of patients with known or highly suspected relapse will improve the PPV. However, ^{18}F-FDG PET is only clinically useful if relapse is not definitively known before the patient undergoes the functional imaging studies. Short follow-up will be in favor of a better NPV. To allow comparison between studies, it may be indicated to report 6-month and 1-year progression-free survival data. Most studies are oversimplified by reporting only positive or negative PET findings. However, in routine practice, it is not unusual to be confronted with questionable findings. Only 2 studies discussed this issue.[43,85] Both studies found a higher accuracy if questionable lesions are analyzed as negative findings. We have some doubt in our center that accuracy is the most important issue. From a clinical point

Table 6 Predictive Value of Whole-Body ^{18}F-FDG PET for Post-Treatment Evaluation in NHL (Adapted from Jerusalem and Hustinx[19])

Authors	Median Follow-Up (Months)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Mikhaeel et al[53]	30	60% (9/15)	100% (30/30)	100% (9/9)	83% (30/36)	87% (39/45)
Spaepen et al[80]	21	70% (26/37)	100% (56/56)	100% (26/26)	84% (56/67)	88% (82/93)
Overall		67% (35/52)	100% (86/86)	100% (35/35)	83% (86/103)	88% (121/138)

of view we are in favor of a more sensitive interpretation, allowing earlier salvage therapy in the case of residual disease. To improve specificity we correlate in a second time our findings with clinical informations and other imaging modalities encouraging also, whenever possible, a multidisciplinary interpretation.

Response Assessment After Radioimmunotherapy (RIT)

RIT is a new treatment option in NHL. The antitumor mechanism is based on immunologic effects and radiation damage. Torizuka and coworkers[86] showed in a small study population (14 low- or intermediate-grade NHL) that ^{18}F-FDG PET findings obtained 1 to 2 months after RIT correlated well with the ultimate best response of NHL to RIT. In contrast, earlier ^{18}F-FDG PET findings 5 to 7 days after RIT may fail to reliably assess the long-term therapeutic effect. Further studies are clearly warranted before using ^{18}F-FDG PET routinely for monitoring response to RIT.

References

1. Front D, Israel O: The role of Ga-67 scintigraphy in evaluating the results of therapy of lymphoma patients. Semin Nucl Med 25:60-71, 1995
2. Jerusalem G, Hustinx R, Beguin Y, et al: PET scan imaging in oncology. Eur J Cancer 39:1525-1534, 2003
3. Rini JN, Manalili EY, Hoffman MA, et al: F-18 FDG versus Ga-67 for detecting splenic involvement in Hodgkin's disease. Clin Nucl Med 27:572-577, 2002
4. Kostakoglu L, Leonard JP, Kuji I, et al: Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. Cancer 94:879-888, 2002
5. Wirth A, Seymour JF, Hicks RJ, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography, gallium-67 scintigraphy, and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. Am J Med 112:262-268, 2002
6. Bar-Shalom R, Yefremov N, Haim N, et al: Camera-based FDG PET and 67Ga SPECT in evaluation of lymphoma: Comparative study. Radiology 227:353-360, 2003
7. Friedberg JW, Fischman A, Neuberg D, et al: FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: A blinded comparison. Leuk Lymphoma 45:85-92, 2004
8. Sasaki M, Kuwabara Y, Koga H, et al: Clinical impact of whole body FDG-PET on the staging and therapeutic decision making for malignant lymphoma. Ann Nucl Med 16:337-345, 2002
9. Shen YY, Kao A, Yen RF: Comparison of 18F-fluoro-2-deoxyglucose positron emission tomography and gallium-67 citrate scintigraphy for detecting malignant lymphoma. Oncol Rep 9:321-325, 2002
10. Van Den Bossche B, Lambert B, De Winter F, et al: 18FDG PET versus high-dose 67Ga scintigraphy for restaging and treatment follow-up of lymphoma patients. Nucl Med Commun 23:1079-1083, 2002
11. Jerusalem G, Beguin Y, Fassotte MF, et al: Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 94:429-433, 1999
12. Jerusalem G, Beguin Y, Fassotte MF, et al: Early detection of relapse by whole-body positron emission tomography (PET) in the follow-up of patients with Hodgkin's disease (HD). Ann Oncol 14:123-130, 2003
13. Elstrom R, Guan L, Baker G, et al: Utility of FDG-PET scanning in lymphoma by WHO classification. Blood 101:3875-3876, 2003
14. Jerusalem G, Warland V, Najjar F, et al: Whole-body 18F-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. Nucl Med Commun 20:13-20, 1999
15. Jerusalem G, Beguin Y, Najjar F, et al: Positron emission tomography (PET) with ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) for the staging of low grade non-Hodgkin's lymphoma (NHL). Ann Oncol 825-830, 2001
16. Jerusalem G, Beguin Y, Fassotte MF, et al: Whole-body positron emission tomography using 18F-fluorodeoxyglucose compared to standard procedures for staging patients with Hodgkin's disease. Haematologica 86:266-273, 2001
17. Jerusalem G, Beguin Y: Positron emission tomography in non-Hodgkin's lymphoma (NHL): Relationship between tracer uptake and pathological findings, including preliminary experience in the staging of low-grade NHL. Clin Lymphoma 3:56-61, 2002
18. Dobert N, Menzel C, Hamscho N, et al: Atypical thoracic and supraclavicular FDG-uptake in patients with Hodgkin's and non-Hodgkin's lymphoma. Q J Nucl Med Mol Imaging 48:33-38, 2004
19. Jerusalem G, Hustinx R: Nuclear Medicine, in Canellos G, Lister TA, Young B (eds): The Lymphomas (ed 2). New York, Elsevier (in press)
20. Zijlstra JM, Hoekstra OS, Raijmakers PG, et al: 18FDG positron emission tomography versus 67Ga scintigraphy as prognostic test during chemotherapy for non-Hodgkin's lymphoma. Br J Haematol 123:454-462, 2003
21. Jerusalem G, Warland V, Beguin Y, et al: Accuracy of end of treatment 18F-FDG PET for predicting relapse in patients with Hodgkin's disease (Hd) and non-Hodgkin's lymphoma (Nhl). Proc Am Soc Clin Oncol 22:572, 2003 (abstr 2299)
22. Mikosch P, Gallowitsch HJ, Zinke-Cerwenka W, et al: Accuracy of whole-body 18F-FDG-PET for restaging malignant lymphoma. Acta Med Austr 30:41-47, 2003
23. Hueltenschmidt B, Sautter-Bihl ML, Lang O, et al: Whole body positron emission tomography in the treatment of Hodgkin disease. Cancer 91:302-310, 2001
24. Bangerter M, Moog F, Griesshammer M, et al: Role of whole body FDG-PET imaging in predicting relapse of malignant lymphoma in patients with residual masses after treatment. Radiography 5:155-163, 1999
25. 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 98:2930-2934, 2001
26. Panizo C, Perez-Salazar M, Bendandi M, et al: Positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual Hodgkin's disease mediastinal masses. Leuk Lymphoma 45:1829-1833, 2004
27. Glatz S, Kotzerke J, Moog F, et al: Vortauschung eines mediastinalen Non-Hodgkin-Lymphomrezidivs durch diffuse Thymushyperplasie im 18F-FDG-PET. Fortschr Rontgenstr 165:309-310, 1996
28. Weinblatt ME, Zanzi I, Belakhlef A, et al: False-positive FDG-PET imaging of the thymus of a child with Hodgkin's disease. J Nucl Med 38:888-890, 1997
29. Sandherr M, von Schilling C, Link T, et al: Pitfalls in imaging Hodgkin's disease with computed tomography and positron emission tomography using fluorine-18-fluorodeoxyglucose. Ann Oncol 12:719-722, 2001
30. de Wit M, Bumann D, Beyer W, et al: Whole-body positron emission tomography (PET) for diagnosis of residual mass in patients with lymphoma. Ann Oncol 8:S57-S60, 1997 (suppl 1)
31. Cremerius U, Fabry U, Neuerburg J, et al: Positron emission tomography with 18F-FDG to detect residual disease after therapy for malignant lymphoma. Nucl Med Commun 19:1055-1063, 1998
32. Weidmann E, Baican B, Hertel A, et al: Positron emission tomography (PET) for staging and evaluation of response to treatment in patients with Hodgkin's disease. Leuk Lymph 34:545-551, 1999
33. de Wit M, Bohuslavizki KH, Buchert R, et al: 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. Ann Oncol 12:29-37, 2001
34. Yoon SN, Park CH, Kim MK, et al: False-positive F-18 FDG gamma camera positron emission tomographic imaging resulting from inflammation of an anterior mediastinal mass in a patient with non-Hodgkin's lymphoma. Clin Nucl Med 26:461-462, 2001

35. Zinzani PL, Fanti S, Battista G, et al: Predictive role of positron emission tomography (PET) in the outcome of lymphoma patients. Br J Cancer 91:850-854, 2004
36. Dittmann H, Sokler M, Kollmannsberger C, et al: Comparison of 18FDG-PET with CT scans in the evaluation of patients with residual and recurrent Hodgkin's lymphoma. Oncol Rep 8:1393-1399, 2001
37. de Hemricourt E, De Boeck K, Hilte F, et al: Sarcoidosis and sarcoid-like reaction following Hodgkin's disease. Report of two cases. Mol Imaging Biol 5:15-19, 2003
38. Bomanji JB, Syed R, Brock C, et al: Challenging cases and diagnostic dilemmas: Case 2. Pitfalls of positron emission tomography for assessing residual mediastinal mass after chemotherapy for Hodgkin's disease. J Clin Oncol 20:3347-3349, 2002
39. Naumann R, Beuthien-Baumann B, Fischer R, et al: Simultaneous occurence of Hodgkin's lymphoma and eosinophilic granuloma—a potential pitfall in PET imaging. Clin Lymphoma 3:121-124, 2002
40. Cheong KA, Rodgers NG, Kirkwood ID: Erythema nodosum associated with diffuse, large B-cell non-Hodgkin lymphoma detected by FDG PET. Clin Nucl Med 28:652-654, 2003
41. Becherer A, Mitterbauer M, Jaeger U, et al: Positron emission tomography with [18F]2-fluoro-D-2-deoxyglucose (FDG-PET) predicts relapse of malignant lymphoma after high-dose therapy with stem cell transplantation. Leukemia 16:260-267, 2002
42. Lorenzen J, de Wit M, Buchert R, et al: Granulation tissue: pitfall in therapy control with F-18-FDG PET after chemotherapy. Nuklearmedizin 38:333-336, 1999
43. Naumann R, Vaic A, Beuthien-Baumann B, et al: Prognostic value of positron emission tomography in the evaluation of post-treatment residual mass in patients with Hodgkin's disease and non-Hodgkin's lymphoma. Br J Haematol 115:793-800, 2001
44. Armitage JO, Weisenburger DD, Hutchins M, et al: Chemotherapy for diffuse large-cell lymphoma—rapidly responding patients have more durable remissions. J Clin Oncol 4:160-164, 1986
45. Engelhard M, Meusers P, Brittinger G, et al: Prospective multicenter trial for the response-adapted treatment of high-grade malignant non-Hodgkin's lymphomas: Updated results of the COP-BLAM/IMVP-16 protocol with randomized adjuvant radiotherapy. Ann Oncol 2 Suppl 2:177-180, 1991
46. Haq R, Sawka CA, Franssen E, et al: Significance of a partial or slow response to front-line chemotherapy in the management of intermediate-grade or high-grade non-Hodgkin's lymphoma: A literature review. J Clin Oncol 12:1074-1084, 1994
47. Rahmouni A, Tempany C, Jones R, et al: Lymphoma: Monitoring tumor size and signal intensity with MR imaging. Radiology 188:445-451, 1993
48. Front D, Bar-Shalom R, Mor M, et al: Aggressive non-Hodgkin lymphoma: Early prediction of outcome with 67Ga scintigraphy. Radiology 214:253-257, 2000
49. Janicek M, Kaplan W, Neuberg D, et al: 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 15:1631-1637, 1997
50. Gasparini M, Bombardieri E, Castellani M, et al: Gallium-67 scintigraphy evaluation of therapy in non-Hodgkin's lymphoma. J Nucl Med 39:1586-1590, 1998
51. Kaplan WD, 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 8:1966-1970, 1990
52. Romer W, Hanauske AR, Ziegler S, et al: Positron emission tomography in non-Hodgkin's lymphoma: Assessment of chemotherapy with fluorodeoxyglucose. Blood 91:4464-4471, 1998
53. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al: 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leuk Lymphoma 39:543-553, 2000
54. Jerusalem G, Beguin Y, Fassotte MF, et al: Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. Haematologica 85:613-618, 2000
55. Kostakoglu L, Coleman M, Leonard JP, et al: PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. J Nucl Med 43:1018-1027, 2002
56. 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 13:1356-1363, 2002
57. Torizuka T, Nakamura F, Kanno T, et al: Early therapy monitoring with FDG-PET in aggressive non-Hodgkin's lymphoma and Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging 31:22-28, 2004
58. Young H, Baum R, Cremerius U, et al: Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 35:1773-1782, 1999
59. Spaepen K, Stroobants S, Dupont P, et al: [(18)F]FDG PET monitoring of tumour response to chemotherapy: Does [(18)F]FDG uptake correlate with the viable tumour cell fraction? Eur J Nucl Med Mol Imaging 30:682-688, 2003
60. Philip T, Guglielmi C, Hagenbeek A, et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 333: 1540-1545, 1995
61. Anselmo AP, Meloni G, Cavalieri E, et al: Conventional salvage chemotherapy vs. high-dose therapy with autografting for recurrent or refractory Hodgkin's disease patients. Ann Hematol 79:79-82, 2000
62. Spaepen K, Stroobants S, Dupont P, et al: Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. Blood 102:53-59, 2003
63. Cremerius U, Fabry U, Wildberger JE, et al: Pre-transplant positron emission tomography (PET) using fluorine-18-fluoro-deoxyglucose (FDG) predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkin's lymphoma. Bone Marrow Transplant 30:103-111, 2002
64. Schot B, van Imhoff G, Pruim J, et al: Predictive value of early 18F-fluoro-deoxyglucose positron emission tomography in chemosensitive relapsed lymphoma. Br J Haematol 123:282-287, 2003
65. Filmont JE, Czernin J, Yap C, et al: Value of F-18 fluorodeoxyglucose positron emission tomography for predicting the clinical outcome of patients with aggressive lymphoma prior to and after autologous stem-cell transplantation. Chest 124:608-613, 2003
66. Coiffier B: How to interpret the radiological abnormalities that persist after treatment in non-Hodgkin's lymphoma patients? Ann Oncol 10: 1141-1143, 1999
67. Radford JA, Cowan RA, Flanagan M, et al: The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease. J Clin Oncol 6:940-946, 1988
68. Glenn LD, Kumar PP: The residual mediastinal mass following radiation therapy for Hodgkin's disease. Am J Clin Oncol 14:16-24, 1991
69. Coiffier B, Gisselbrecht C, Vose JM, et al: Prognostic factors in aggressive malignant lymphomas: Description and validation of a prognostic index that could identify patients requiring a more intensive therapy. The Groupe d'Etudes des Lymphomes Agressifs. J Clin Oncol 9:211-219, 1991
70. Jochelson M, Mauch P, Balikian J, et al: The significance of the residual mediastinal mass in treated Hodgkin's disease. J Clin Oncol 3:637-640, 1985
71. Israel O, Front D, Lam M, et al: Gallium 67 imaging in monitoring lymphoma response to treatment. Cancer 61:2439-2443, 1988
72. Surbone A, Longo DL, DeVita VT Jr, et al: Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: Significance and management. J Clin Oncol 6:1832-1837, 1988
73. Canellos GP: Residual mass in lymphoma may not be residual disease. J Clin Oncol 6:931-933, 1988
74. Segall GM: FDG PET imaging in patients with lymphoma: A clinical perspective. J Nucl Med 42:609-610, 2001
75. Zinzani PL, Magagnoli M, Chierichetti F, et al: The role of positron

emission tomography (PET) in the management of lymphoma patients. Ann Oncol 10:1181-1184, 1999
76. Mikhaeel NG, Timothy AR, Hain SF, et al: 18-FDG-PET for the assessment of residual masses on CT following treatment of lymphomas. Ann Oncol 11:S147-S150, 2000
77. Foo SS, Mitchell PL, Berlangieri SU, et al: Positron emission tomography scanning in the assessment of patients with lymphoma. Intern Med J 34:388-397, 2004
78. Spaepen K, Stroobants S, Dupont P, et al: Can positron emission tomography with [18F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity? Br J Haematol 115:272-278, 2001
79. Guay C, Lepine M, Verreault J, et al: Prognostic value of PET using 18F-FDG in Hodgkin's disease for posttreatment evaluation. J Nucl Med 44:1225-1231, 2003
80. Spaepen K, Stroobants S, Dupont P, et al: Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: Is [18F]FDG-PET a valid alternative to conventional diagnostic methods? J Clin Oncol 19:414-419, 2001
81. Maisey NR, Hill ME, Webb A, et al: Are 18fluorodeoxyglucose positron emission tomography and magnetic resonance imaging useful in the prediction of relapse in lymphoma residual masses? Eur J Cancer 36:200-206, 2000
82. Cremerius U, Fabry U, Neuerburg J, et al: Prognostic significance of positron emission tomography using fluorine-18-fluorodeoxyglucose in patients treated for malignant lymphoma. Nuklearmedizin 40:23-30, 2001
83. Lavely WC, Delbeke D, Greer JP, et al: FDG PET in the follow-up management of patients with newly diagnosed Hodgkin and non-Hodgkin lymphoma after first-line chemotherapy. Int J Radiat Oncol Biol Phys 57:307-315, 2003
84. Lang O, Bihl H, Hultenschmidt B, et al: Clinical relevance of positron emission tomography (PET) in treatment control and relapse of Hodgkin's disease. Strahlenther Onkol 177:138-144, 2001
85. Cremerius U, Fabry U, Kroll U, et al: Clinical value of FDG PET for therapy monitoring of malignant lymphoma—results of a retrospective study in 72 patients. Nuklearmedizin 38:24-30, 1999
86. Torizuka T, Zasadny KR, Kison PV, et al: Metabolic response of non-Hodgkin's lymphoma to 131I-anti-B1 radioimmunotherapy: Evaluation with FDG PET. J Nucl Med 41:999-1005, 2000
87. Jerusalem G, Hustinx R, Beguin Y, et al: Whole-body positron emission tomography using ^{18}F-fluorodeoxyglucose for staging and response assessment in Hodgkin's disease, in Colombus F (ed): Progress in Hodgkin's Disease Research. Nova Science (in press)