Role of attenuation correction for fluorine-18 fluorodeoxyglucose positron emission tomography in the primary staging of malignant lymphoma

Jörg Kotzerke[1], Albrecht Guhlmann[1], Florian Moog[1], Norbert Frickhofen[2], Sven N. Reske[1]

[1] Department of Nuclear Medicine, University of Ulm, Germany
[2] Department of Internal Medicine, University of Ulm, Germany

Received 1 July and in revised form 19 September 1998

Abstract Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to improve the diagnostic accuracy in the staging of malignant lymphomas, based on the metabolic signal of the lesions. This study was undertaken to determine the effect of attenuation correction in the detection of nodal and extranodal lesions in the primary staging of malignant lymphomas. Fifty-one untreated patients with either non-Hodgkin lymphoma (NHL, *n*=29) or Hodgkin's disease (*n*=22) were retrospectively evaluated. Static FDG-PET imaging of the trunk was performed following administration of 250–350 MBq FDG. Attenuation correction was performed in all patients. Images were reconstructed iteratively with or without transmission scans. Image evaluation was performed independently by two observers, who each examined one set of images (i.e. attenuation-corrected or uncorrected). The final decision as to whether results were discordant was reached by consensus of both observers. Out of 593 evaluated lymph node regions, 187 regions of increased FDG uptake were identified by both techniques. Differences between the readers concerned mainly the anatomical assignment of lesions (*n*=33) or the status (benign/malignant) of individual lesions (*n*=24). However, direct comparison of the two sets of images demonstrated very similar lesion contrast on attenuation-corrected and non-attenuation-corrected images. Real differences could be determined only in five regions (neck, 1; mediastinum, 1; upper abdomen, 3). Thirty-seven extranodal lesions (including lung, liver, spleen, bone marrow and soft tissue) were detected by both techniques without significant differences. It is concluded that in this study, attenuation correction did not improve the diagnostic accuracy of FDG-PET in the detection of lymph node or organ involvement during the primary staging of malignant lyphomas. Of more importance seemed to be the experience of the reader regarding the classification of a lesion's status the anatomical assignment, knowledge of physiological uptake and artefacts, and systematic and skilful examination of all regions scanned.

Key words: Attenuation correction – Fluorine-18 fluorodeoxyglucose positron emission tomography – Lymphoma – Staging – Hodgkin's disease

Eur J Nucl Med (1999) 26:31–38

Correspondence to: J. Kotzerke, Department of Nuclear Medicine, University of Ulm, Robert-Koch-Strasse 8, D-89081 Ulm, Germany

Introduction

In the past few years, positron emission tomography using fluorine-18 fluorodeoxyglucose (FDG-PET) has been increasingly recognized as a promising diagnostic procedure for functional imaging. Its use is based on the observation that cells which have undergone malignant transformation are characterized by an elevated glucose metabolism that can be demonstrated with PET [1, 2]. The decisive advantage of this technique is that it allows characterization of tissue essentially independent of morphological parameters. FDG-PET has brought about a major improvement in tumour staging in a variety of malignant diseases. In lymphoma, FDG-PET is superior to conventional imaging techniques not only for the detection of malignant lymph nodes, but also in the definition of extranodal disease (e.g. liver, spleen and bone marrow) [3–8]. Other, more pathophysiologically oriented studies have documented a correlation between the intensity of FDG uptake and the degree of malignancy of individual types of lymphoma [9–12]. Recent therapeutic strategies are based on the exact definition of tumour spread, stressing the importance of a precise staging modality.

Multiple consecutive FDG-PET scans can be restored to a whole-body scan [13, 14], giving a fast and accurate overview in three directions. However, there is controversy over whether attenuation correction is needed. A further question is whether transmission imaging must

be carried out directly prior to emission scanning. This procedure is not only time consuming, but requires exact planning of multiple whole-body scans with a single PET scanner.

Phantom studies without attenuation correction have demonstrated focus distortion [15]. The aim of most PET studies in oncology, however, is to detect or to exclude a malignant lesion and not to determine its size and shape. From clinical experience it is the impression that an emission scan alone might be sufficient for this purpose, but a specific comparison of attenuation-corrected and uncorrected images covering all relevant regions of the body is still lacking. Therefore, in a retrospective study we have compared the accuracy of non-attenuation-corrected and attenuation-corrected FDG-PET images with regard to nodal and extranodal lesion detection in untreated patients with Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL).

Materials and methods

Between July 1992 and October 1995, 60 consecutive patients with biopsy-proven and untreated lymphoma were enrolled in an FDG-PET study [16]. The PET data of 51 patients could be reanalysed to compare the effect of attenuation correction in the detection of small lesions. Twenty-two patients suffered from HD: 12 patients showed histology suggesting nodular sclerosis, eight mixed cellularity and two lymphocytic predominance. Of the 29 patients with NHL, eight had low-grade, four intermediate-grade and 17 high-grade disease according to the Working Formulation [17]. The 30 females and 21 males ranged in age from 11 to 72 years (median 37 years). All patients gave their informed consent before being enrolled into the study.

PET studies were obtained using a Siemens-CTI-ECAT Scanner 931/08/12. The scanner simultaneously acquires 15 contiguous transverse sections of 6.75 mm covering 10.1 cm of the long axis of the patient (one bed position). Patients had to fast for at least 8 hours prior to the examination. FDG, synthesized according to standard protocols, was injected intravenously at a mean dose of 300 MBq (range 250–350 MBq). Diuresis was stimulated (20 mg furosemide) to reduce the intensity of the urinary activity.

Static emission scans from the base of the skull to the lower pelvis, in seven cases including the proximal femora and in one case the lower legs were obtained 50–60 min after FDG administration. This required scanning in five to eight bed positions with an acquisition time of 15 min each. For attenuation correction, transmission scans were acquired using a germanium-68/gallium-68 external ring source prior to FDG injection. Ten-minute transmission scans per bed position were performed in five to eight bed positions on the same day prior to the emission scan (n=13) or on another day (n=38). Patients were carefully repositioned by reference to laser-guided landmarks so as to ensure an identical field of view for emission and transmission scanning. Between the two sets of emission scans patients were allowed to move. Images were reconstructed with an iterative reconstruction algorithm [18] either including or not including the transmission data. The in-plane resolution (full-width at half-maximum) for iterative reconstruction was 7 mm in the centre of the field of view.

Evaluation of PET studies was done "blind" by visual interpretation, independently by two board-certified nuclear medicine physicians. Transaxial, coronal and sagittal sections were reviewed on film in a standardized manner. Any foci with a significant increase in FDG uptake in comparison to surrounding tissue were considered to be suspicious for lymphoma. These visual findings were graded on a five-point scale (1=lymphoma definitely present, 2=lymphoma probably present, 3=equivocal, 4=lymphoma probably absent, 5=lymphoma definitely absent). Areas classified as "1" and "2" were considered positive for lymphoma and grouped. Areas classified as "4" and "5" were considered negative for lymphoma and grouped as well. The final decision as to whether discordant results were obtained with and without attenuation correction was reached by consensus of both observers. The final evaluation of areas with different FDG uptake was done by comparison of both image sets to detect even minor differences due to the reconstruction procedure. Differences in assessment were attributed to differences in the anatomical assignment, differences in classification (benign or malignant) or differences due to

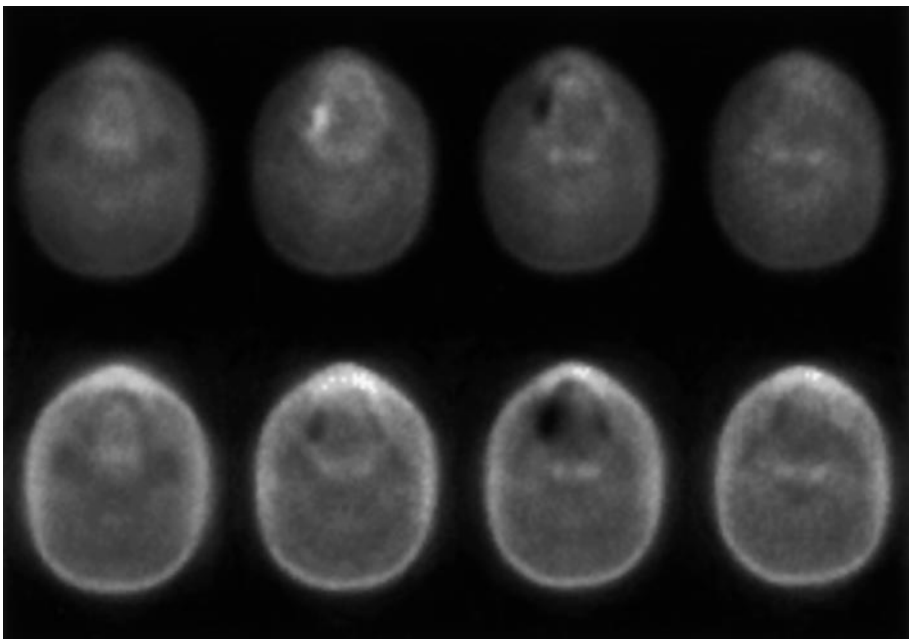

Fig. 1. Series of attenuation-corrected (*upper row*) and uncorrected (*lower row*) transaxial FDG-PET images of the upper jaw in a 37-year-old man with NHL. The intense uptake on the attenuation-corrected images is caused by misalignment of emission and transmission data. The photon-deficient area is due to a metal implant

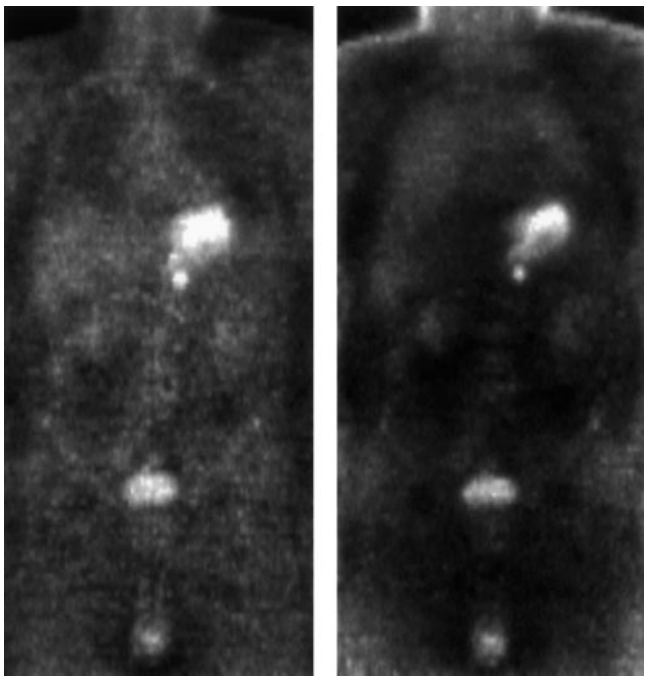

Fig. 2. Attenuation-corrected (*left*) and uncorrected (*right*) coronal FDG-PET images in a 58-year-old man with NHL. Thoracic CT did not reveal an enlarged lymph node

attenuation correction. Quantitative analysis of FDG uptake was not performed. The degree of agreement between the two readers was measured with the κ statistic (κ equals 0 when there is chance agreement and 1 when there is perfect agreement).

Results

Of 593 lymph node regions examined, 406 showed normal glucose metabolism while 187 demonstrated increased uptake. With regard to these 187 regions, there were differences in the anatomical assignment by the two readers (e.g. supra- or infraclavicular region, mesenteric or para-aortal region) in 33 cases although agreement existed about the status of the lesions in question. Most of these discrepancies related to the differentiation of mediastinal and hilar lymph nodes, which belong to the same area according to the definition of the German Hodgkin Study Group. In a further 24 regions there was disagreement about the status of individual lesions (e.g. unspecific, inflammatory or malignant) although there was concordance as to the localization. In 17 of these 24 cases one reader classified the lesion as benign while the other reader classified it as equivocal; inthe other seven cases one reader classified the lesion as equivocal while the other reader classified it as malignant. In only five cases could real differences be determined and related to attenuation correction. These five cases comprised one instance of soft tissue uptake (Fig. 1), one of infraclavicular FDG accumulation (Fig. 2), and three cases of different lesion contrast of hepatic hilar and splenic hilar lymph nodes (Figs. 3–5). There was strong agreement between the two readers concerning the assessment of malignancy (κ=0.90) and regional definition (κ=0.86). Nearly perfect agreement existed with regard to the lesion detection using attenuation- and non-attenuation-corrected images (κ=0.98).

A total of 37 extranodal lymphomatous manifestations were detected concordantly with and without attenuation correction. Confirmation of organ involvement was established by means of computed tomography (CT), magnetic resonance imaging (MRI), or biopsy as described in detail elsewhere [5, 6]. These manifestations included involvement of the bone marrow (*n*=13), the spleen (*n*=12), the lungs (*n*=4), the liver (*n*=2), soft tissue (*n*=3), bowel (*n*=2) and kidneys (*n*=1). Despite the changes caused by attenuation correction, small lung (Fig. 6) and bone marrow lesions (Fig. 7) were clearly

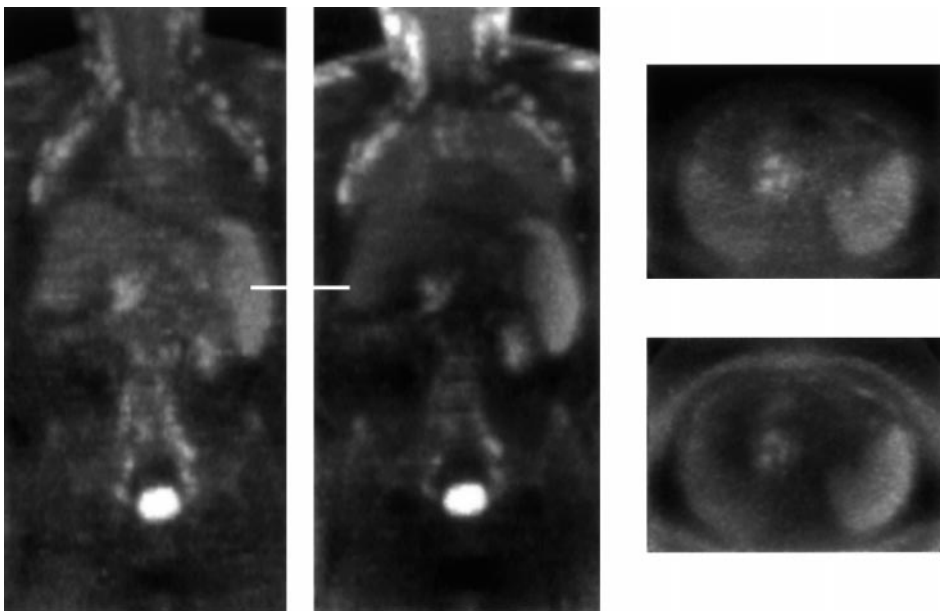

Fig. 3. Attenuation-corrected (*left*) and uncorrected (*middle*) coronal FDG-PET images in a 47-year old man with NHL (stage 4 S: involvement of spleen and bone marrow). On the corrected images a small lesion could be identified in the hilum of the spleen which was not visible on the uncorrected images (*right down*). The level of the transversal slices (*right*) is indicated (*white line*)

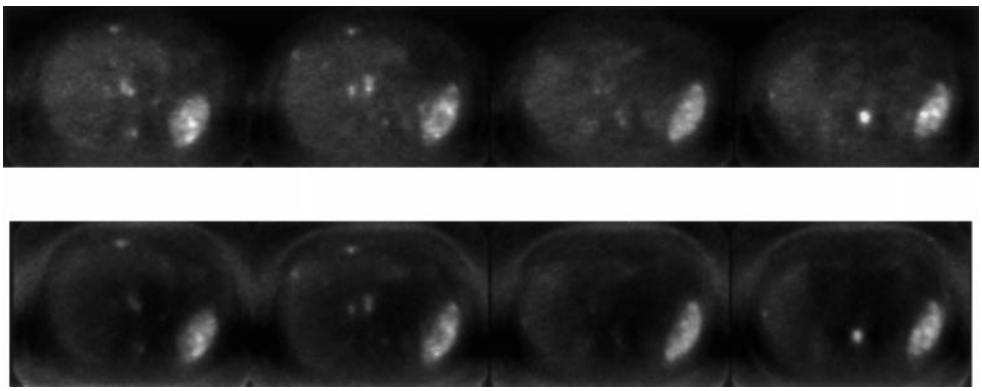

Fig. 4. Series of attenuation-corrected (*upper row*) and uncorrected (*lower row*) transaxial FDG-PET images of the liver in a 46-year-old man with NHL (stage 4 S: involvement of the liver, bone marrow and spleen)

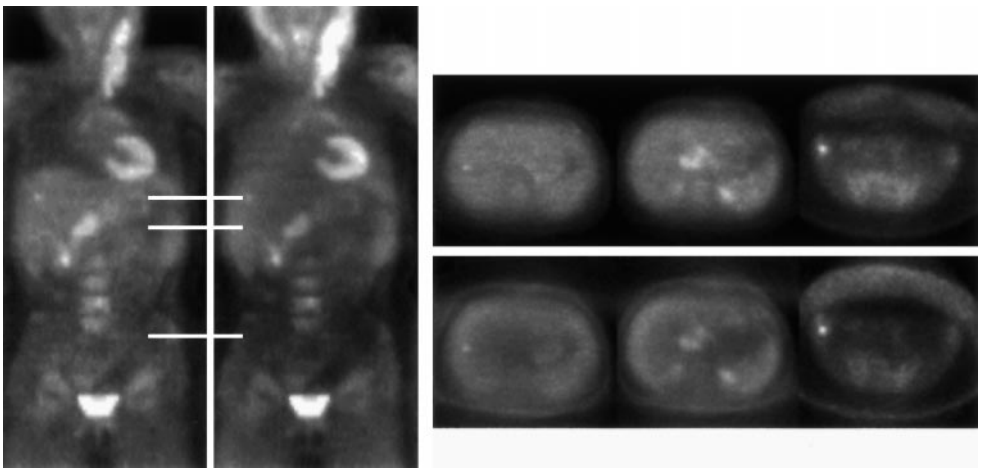

Fig. 5. Attenuation corrected (*left*) and uncorrected (*middle*) coronal FDG-PET images in an 11-year-old girl with Hodgkin's disease (stage 4: involvement of liver and bone marrow). The small liver lesion (0.9 cm, histologically proven) as well as bone marrow involvement in the spine could be recognized on both sets of images. The lymph nodes at the hilum of the liver are better visualized on the attenuation corrected images. The level of the transversal slices (*right*) is indicated (*while lines*)

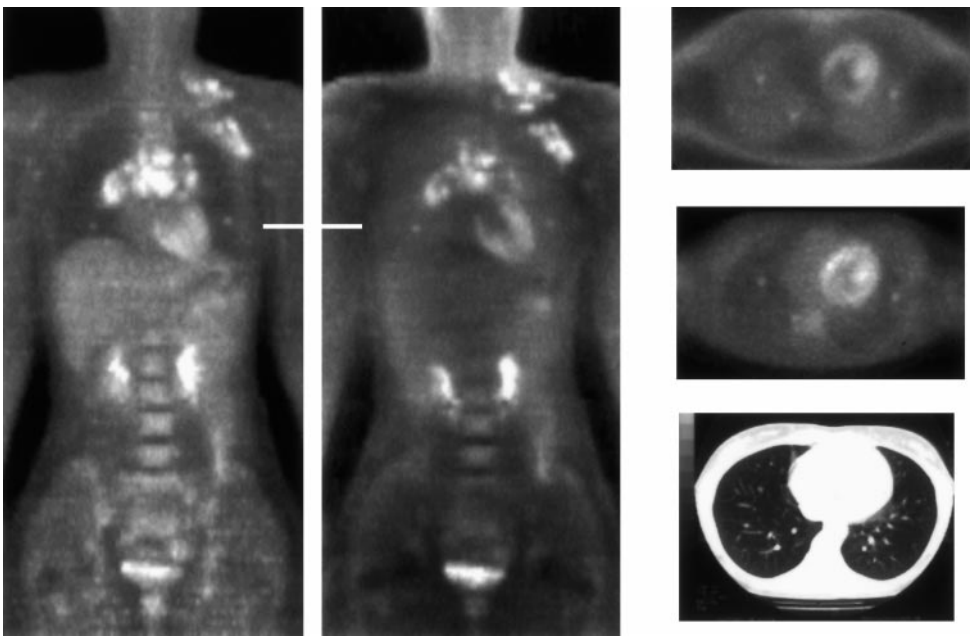

Fig. 6. Attenuation-corrected (*left*) and uncorrected (middle) coronal FDG-PET images in a 17-year old girl with HD (stage 4: involvement of lung). The small lung lesions are detectable on both sets of images. Anatomical differentiation of the left-sided axillary lymph nodes from the lungs was possible with both techniques. The level of the transversal slices (*right*) is indicated (*while lines*)

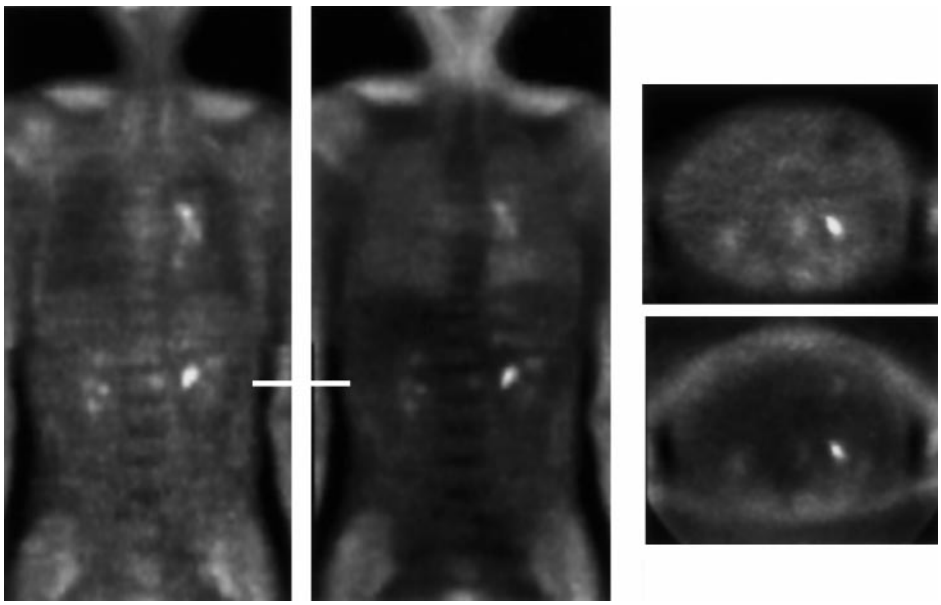

Fig. 7. FDG-PET images obtained in a 22-year-old male with HD of nodular sclerosis histology (stage 4: bone marrow involvement). In addition to mediastinal nodular disease, focal FDG accumulation at L1, indicating lymphomatous infiltration, is clearly demonstradte on attenuation-corrected (*left*) and uncorrected (*middle*) coronal FDG-PET images. The lymphomatous infiltration was verified by MRI, which revealed a hypointense lesion in the left part of the vertebral body with enhancement after gadolinium-DTPA injection using a T1-weighted sequence. The level of the transversal slices (*right*) is indicated (*while lines*)

demonstrated on both attenuation-corrected and non-attenuation-corrected images due to similar lesion contrast.

Discussion

FDG-PET is an effective modality for demonstrating nodal and extranodal involvement in malignant lymphomas even if CT and MRI are inconclusive. This has been demonstrated in a number of studies, in some cases using attenuation correction [4, 6, 9]. It has been assumed that attenuation correction might not be a prerequisite in scanning oncological patients [15], but this hypothesis has never been verified in a larger series of patients by direct comparison of attenuation-corrected and non-attenuation-corrected FDG-PET images.

Non-attenuation-corrected FDG-PET images are characterized by “hot skin” and intense representation of the lungs, whereas attenuation-corrected images demonstrate a more homogeneous activity distribution. Attenuation correction allows quantification of the radioactivity at any point in the body, but an adverse effect is the addition of noise to the information, especially if low-count transmission images are used. This results in the clinical impression that uncorrected images might be simpler and clearer because they include nearly all information but minimal noise.

Intense representation of the skin might influence the detectability of small lesions in lymph node regions near the body surface (e.g. neck, supraclavicular and inguinal regions). In our series, however, lymph node involvement could be demonstrated at the neck and the inguinal region in 42 and 17 areas, respectively, by both techniques. Differences occurred regarding the anatomical assignment (e.g. cervical or supraclavicular region) or the status (benign/malignant) of lesions. Only a single patient revealed a true difference due to a metal implant in the upper jaw; in this case the hot lesion in the attenuation-corrected study was caused by misalignment of the emission and transmission data.

One advantage of attenuation correction might be the clear delineation of the lungs resulting in better differentiation between hilar lymph nodes and intrapulmonary lesions or axillary lymph nodes and pleural lesions. Evaluation of images in three directions allows the exact anatomical localization of lesions in most cases. Differences in anatomical assignment in the mediastinum (Table 1) concerned the differentiation of mediastinal and hilar lymph nodes, which belong to the same area; such differences would not alter staging.

Another critical region was the abdomen. Without anatomical landmarking, lesions are difficult to assign to either mesenteric or para-aortic lymph nodes. However, this problem exists in both non-attenuation-corrected and attenuation-corrected studies. The main difference observed was in respect of the hilar lymph nodes of liver and spleen due to different lesion contrast (Figs. 4–5). In three patients, minor differences could be discerned but did not affect staging. These problems in anatomical assignment might be overcome by image fusion of PET images with CT or MRI images.

The use of attenuation correction might be an advantage in very small lesions. In our series, the smallest bone marrow lesion with the lowest FDG uptake could be detected on non-attenuation-corrected as well as on attenuation-corrected images (Fig. 7). Another example of a small bone marrow lesion clearly visualized with both techniques is demonstrated in Fig. 5. Four cases with negative FDG-PET and positive bone marrow biopsy demonstrated bone marrow involvement neither on attenuation-corrected nor on uncorrected images [6].

Table 1. Distribution of lymph node involvement and causes of different assessments

Lymph node regions	No. of regions involved	Differences in anatomical assignment	Differences in classification (benign or malignant)	Differences due to attenuation correction
Neck or SCL	42	4	4	1
ICL	24	2	2	1
Axillary	19	2	1	0
Mediastinal	29	12	4	0
Retroperitoneal	11	3	4	0
Upper abdominal[a]	18	8	4	3
Iliac	27	2	3	0
Inguinal	17	0	2	0
Total	187	33	24	5

ICL, infraclavicular; SCL, supraclavicular

[a] The upper abdominal lymph node region includes the mesenteric, celiac, hepatic hilar, and splenic hilar lymph nodes

In a phantom study, Bengel et al. demonstrated lung tumour distortion on non-attenuation-corrected images, which showed lesion enlargement in the anterior-posterior direction (i.e. the diameter) of less surrounding tissue [15]. The target to background ratio, however, was higher in the uncorrected images. Minor differences of lession contrast to the background. More important was the localization of a lesion, especially the amount of absorption. Smaller differences were found in the thorax and larger differences in the abdomen and pelvis (i.e. regions with higher absorption). However, these calculations were carried out with filtered backprojection (FBP) and cannot be transferred to iterative reconstruction without further verification. Diederichs et al. have shown that the apparent tumour distortion is reduced by up to 30% using the iterative reconstruction algorithm, compared with FBP [19]. Currently, no clinical studies are available that demonstrate the effect of attenuation correction and different reconstruction algorithms on lesion detection and distortion.

In our study of the analysed cases showed intense lesion uptake and multiple lesions. Our comparison did not include a lesion-by-lesion analysis because for clinical staging of malignant lymphoma it is not important to analyse the number of lesions in one lymph node region, but rather to detect or to exclude the involvement of a region, especially if this could be relevant for staging (e.g. organ involvement). However, if a single lesion occurred as nodal or extranodal involvement, the two techniques were compared regarding differences.

Pathophysiologically oriented studies have documented a correlation between the intensity of FDG uptake and the degree of malignancy of individual types of lymphoma [8, 9, 11]. Therefore, FDG-PET might fail to detect low-grade lymphoma. In the evaluation of bone marrow involvement, FDG-PET was able to detect small lesions not causing a positive bone marrow biopsy [6], but it was negative in four patients with low- or intermediate-grade lymphoma who had biopsy-proven bone marrow involvement. However, in these patients, there was no difference between attenuation-corrected and uncorrected images, both techniques failing to demonstrate the bone marrow involvement.

Attenuation correction is necessary for quantification (standardized uptake value or estimation of the metabolic rate). However, the value of these procedures might be restricted to therapy monitoring [20]. Lesion characterization (e.g. benign, inflammatory, malignant) based solely on SUV is not feasible in most cases; furthermore, FDG uptake is highly variable in high- and low-grade lymphomas. The screening procedure in malignant lymphomas to detect or exclude nodal and extranodal involvement is whole body imaging in multiple static acquisitions. If a lesion is depicted, a dynamic study for quantification of glucose metabolism may be added, but it has to be performed on a different day. However, such quantification, which is limited to one bed position, might be problematic due to heterogeneity of FDG uptake of different lymphoma lesions in primary staging or during therapy response.

Another possible means of attenuation correction is the use of theoretical attenuation values. This method assumes predetermined linear attenuation coefficients and has been applied successfully in the brain [21]. However, this approach is ineffective in the thorax, since the absorption distribution is more complex. This has resulted in the development of various post-injection transmission measurements [22–24]. However, a most recent phantom study demonstrated that this approach overestimated tumour activity by a factor of 1.1 in large tumours, increasing to up to 1.39 in small lesions [25]. Further investigations are necessary to demonstrate the need for and usefulness of this attenuation correction procedure before it enters clinical practice.

Limitations of the study concern the PET scanner (931/08/12), which is not a device of the latest genera-

tion. Higher spatial resolution might influence the results. In our series, transmission and emission data were acquired on the same day in only 13 of 51 patients. However, the problem of misalignment can only be overcome by simultaneous acquisition of transmission and emission data. Furthermore, the iterative reconstruction algorithm used was not supplied with the PET scanner and other centres might still use FBP. Since each of the two readers analysed only one set of images, the results were influenced by the individual experience of the readers. However, interobserver agreement was strong for the assessment of malignancy and regional definition (κ=0.90 and 0.86, respectively). Every single difference regarding a lymph node area (which could cause a change in staging) was analysed and the differences were attributed to the various causes listed in Table 1. As regards the differences due to attenuation correction, it remained unresolved whether a lesion was false-positive on attenuation-corrected images (Fig. 3) or false-negative on non-attenuation-corrected images. In a clinical setting, however, clarification of such lesions by biopsy is unethical if there is evidence of other organ involvement.

It is necessary to bear in mind that image quality is affected by various factors such as sensitivity and resolution of the PET scanner, amount of injected radioactivity, scan time, 2D or 3D acquisition (statistics), interval between injection and scanning, the reconstruction algorithms used, the quality and alignment of the transmission scan, and motion artefacts. Furthermore, the clinical experience of an observer in detecting lesions and recognizing artefacts will strongly influence the assessment of FDG-PET images [26–28].

In conclusion, the agreement between attenuation- and non-attenuation-corrected images was higher than the agreement between the two readers regarding the anatomical assignment and the assessment of a lesion's status. Differences following attenuation correction occurred in only 5 of 187 lymph node areas with increased FDG uptake. With regard to organ involvement, no differences were observed. No case of false-positive FDG uptake could be attributed to the lack of attenuation correction. Therefore, we conclude that in this study on the primary staging of malignant lymphoma with whole-body FDG-PET, attenuation correction had only a negligible value.

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