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Positron Emission Tomography for the Staging of Hodgkin's Lymphoma

Increasing the Body of Evidence in Favor of the Method

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The staging of Hodgkin's lymphoma (HL) is crucial for an optimal therapy, and fluorine-18-deoxyglucose-positron emission tomography (FDG-PET) is increasingly used in this regard. However, there is still a scarcity of available data on the staging of HL. Twenty-eight consecutive patients with newly diagnosed HL were included in this study. PET results were compared with conventional staging, including clinical workup, computerized tomography (CT) and sonography. Evaluation was focused on the description of involved lymph node (LN) regions or organs rather than on a lesion-by-lesion analysis. In supradiaphragmal LN, the results of PET and CT scans were positive in 26% and negative in 68% of cases. Furthermore, PET was positive in 5% (CT negative), and CT showed enlarged LN in 1% of cases (PET negative). In infradiaphragmal LN, PET/CT results were positive in 10% and negative in 88% of cases. In 2% of cases, PET showed additional foci, while in 1% the CT was positive. PET changed the staging in 21% of cases (4 up-stagings, 2 down-stagings) and this was confirmed during follow-up. PET should therefore be routinely used for staging HL until larger clinical studies can demonstrate patients who may not require this additional investigation or those patients who are reliably staged on the basis of PET alone.

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Today, the therapeutic approach to Hodgkin's lymphoma (HL) is cure. Standard therapeutic regimens, however, are subject to frequent updating and advances. HL is usually treated with chemotherapy (CHT) with or without additional radiation therapy (RT). The latter may be applied alone in the very early stages of the disease, while it is often combined with CHT in the advanced or refractory stages (1).

The appropriate therapy relies on exact staging, which until recently has been done by sonography and computerized tomography (CT). A major criterion of these morphologic techniques measuring tumor or lymph node involvement is simply the size of a lesion. Minimally affected lymph nodes of normal size or those that are obscured because of insufficient contrast to the surrounding tissue may therefore be missed.

Positron emission tomography (PET) using fluorine-18-deoxyglucose (FDG) has become a widely accepted tool for the staging of HL and its therapy control (2). A recently published prospective trial also showed the sensitivity of PET (88%) to be superior to that of CT (74%) in 22 newly diagnosed HL cases (3).

This study was conducted to further examine the role of PET in the staging of primary HL.

MATERIAL AND METHODS

In 28 consecutive patients (mean age 39 years, range 17–65 years. M:F = 19:9) a PET scan was included into the initial staging of HL. All patients had histopathological verification of the disease and a routine work-up including a CT of the thorax and abdomen. Cervical lymph nodes (LNs) were investigated by CT or sonography. The CT scans were done in several institutions using different scanners. In all cases but one, the CT was done using contrast media. The criteria for nodal tumor burden were also the shape and size (above 1.5 cm within the pelvis and above 1 cm otherwise) of LNs. On the basis of the clinical investigation and the imaging results a clinical staging according to the Ann Arbor classification was done prior to PET. Details of the patients are presented in Table 1.

Whole-body FDG-PET was carried out using a dedicated PET scanner (ECAT Exact 47, Siemens CTI,

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Table 1

Histopathologic subtypes and staging of the patients prior to PET

Subtypes	
Nodular sclerosis	17
Mixed cellularity	4
Lymphocyte rich	5
Lymphocyte depleted	–
Not classified	2
Clinical stage	
I	10
II	14
III	3
IV	1
B Symptoms	
Yes	5
No	23

Knoxville, TN, USA). This device allows the simultaneous acquisition of 47 contiguous slices at a thickness of 3.37 mm each, thus resembling an axial field-of-view of 16.2 cm. The patients were scanned between the base of the skull and the proximal femora, representing 5–7 individual bed positions per patient.

All patients fasted for more than 6 h prior to the examination, to assure optimal conditions for the metabolism of the 18F-FDG, which was provided by commercial sources. Blood glucose levels were checked as being within normal limits before the substance was administered.

Per bed position, a 7-min emission scan followed by a 3-min transmission scan were carried out starting in the femoral/pelvis region. Acquisition was started no earlier than 45 to 60 min after tracer injection. An iterative algorithm (OSEM, 2 iterations, 8 subsets) was used for reconstruction of the images since 09/2000. Prior to 09/2000, a filtered back projection was used for reconstruction. All sagittal, axial and coronal slices as well as an interactive evaluation on the work station were included in the diagnostic process. For the evaluation of the results, two experienced nuclear medicine physicians used a consensus approach.

Two sets of evaluations were made: one as part of the standard staging including only available data from a clinical, bioptic and radiological staging. Involved sites were scored according to CT results, when available, and according to clinical/sonographical information in those patients in whom cervical and/or inguinal LNs were not fully covered by the CT. The other approach was represented by the qualitative evaluation of the PET scan alone. No further quantitative measurements were done. We used an identical approach in both evaluations, evaluating anatomical LN regions and organ sites as described in Table 2.

Table 2

Scheme for the evaluation of tumor sites

Right side	Left side
Cervical	Cervical
Supra-/retro-/infraclavicular	Supra-/retro-/infraclavicular
Axillary	Axillary
Mediastinal/hilar	
Upper abdominal	
Para-aortal	
Iliac	Iliac
Inguinal	Inguinal
Plus lungs, liver, spleen, bone marrow	

RESULTS

A total of 224 supradiaphragmal LN regions were evaluated. In 58 regions (26%) both the standard staging using clinical investigation, sonography and CT and the results of the PET investigation were positive. In 153 (68%) both approaches showed negative results. In 13 regions different results were obtained, showing tumor-like tracer uptake in the FDG-PET in 11 regions (5%), while with the standard approach no abnormal LNs were described. There were also two sites (1%) showing enlarged LNs with normal FDG uptake.

In 168 infradiaphragmal LN regions 16 (10%) were positive with both approaches, while 147 (88%) were normal in all tests. Divergent results were obtained in five regions, showing a positive PET in three (2%) and a positive CT in two (1%) regions.

With respect to the involvement of organs, 168 regions (both lungs, liver, spleen, bone marrow) were investigated which were normal in 160 cases in both tests and correspondingly positive in 4 cases (2%). This includes two tumor affections within the lungs correctly detected by CT and PET and three tumors within the spleen, all clearly detected by PET and seen by CT in two cases only. A further three cases were detected by PET with possible bone marrow infiltration. As shown in Table 1 17/28 (61%) cases presented with nodular-sclerosis of HL and 5/28 (17%) with a lymphocyte-rich HL and 4/28 (14%) showing HL of mixed cellularity. The initial tumor stage according to the Ann Arbor classification was I in 36% and II in 50% of cases. Three cases presented with stage III tumors and one case with stage IV disease.

According to the PET scans, the staging changed in six cases (21%), leading to an upstaging in four patients and to a downstaging in two cases.

One patient initially showed an inguinal LN that was histopathologically positive for HL and the PET scan demonstrated tumor typical metabolism in the mediastinum also. The thoracic CT scan was normal; the patient was upstaged to IIIA and treated with 4 cycles according to the EBOEP scheme and RT. The EBOEP

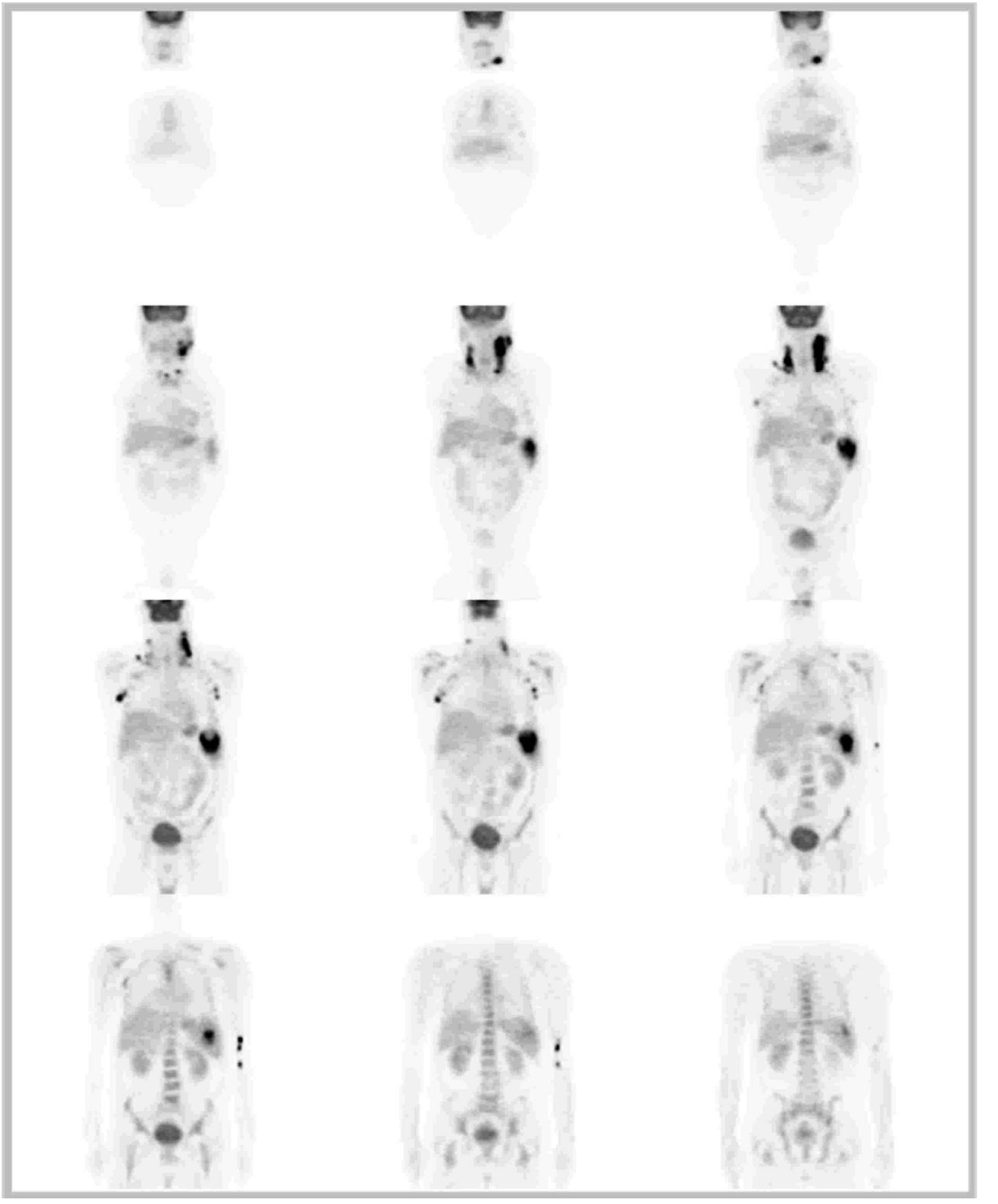

Fig. 1.

scheme consisted of epirubicine 40 mg /m^2 i.v. days 1 + 8, bleomycine 8 mg/m^2 i.v. days 1 + 8, vincistine 2 mg day 1 + 8, etoposide 100 mg/m^2 i.v. days 1–4 and prednisolone 40 mg/m^2 orally days 1–8. Cycles of this scheme were repeated every 3 wk. One of the patients initially showed LN involvement of cervical and mediastinal regions, leading to IIA stage disease. PET confirmed these tumor sites but detected tumor within the spleen that was not described by an earlier CT scan. This led to stage III AS (Fig. 1a, b).

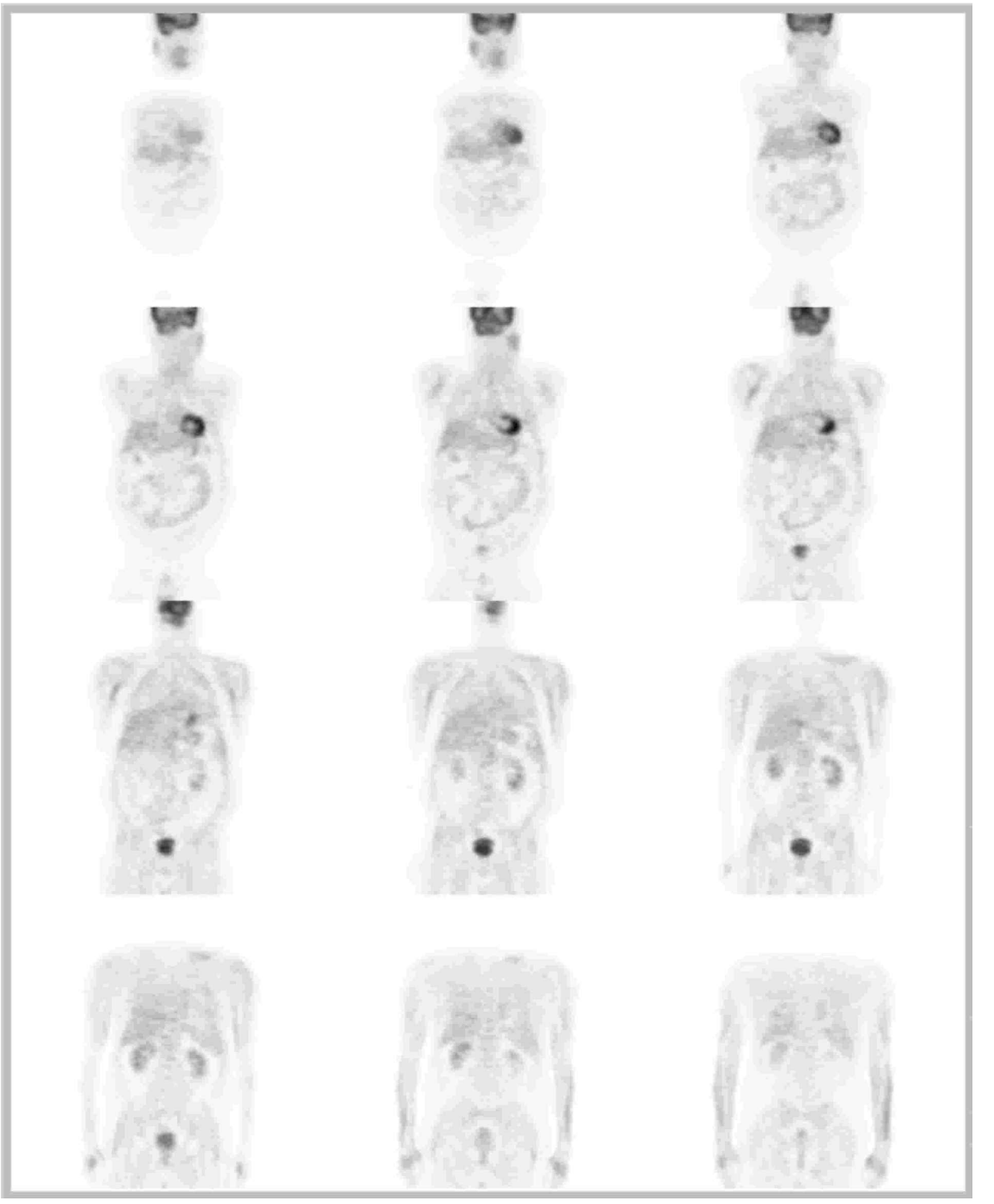

Fig. 1. Series of coronal slices in Hodgkin's lymphoma (HL) Stage III S with bilateral cervical, axillary and splenic involvement: (a) prior to and (b) after chemotherapy.

One patient with widespread abdominal LN involvement that was correctly detected by CT and PET had further sites of high FDG uptake in mediastinal and infraclavicular lymph nodes that were missed by the CT scan. The patient was accordingly upstaged from IIB to IIIB.

In another patient, with supradiaphragmal HL IIB, an abdominal LN focus was described by PET that could not

be confirmed by other methods. This patient received 4 cycles according to the EBOEP protocol. Prior to RT, restaging was done including a follow-up PET, which showed a complete remission (CR).

In one patient suffering from nodular sclerosing HL of inguinal/iliac LN, the CT work-up detected three retroangular, bilateral LNs of suspicious size (>1 cm). The FDG-PET revealed only tumor-like uptake within the inguinal/iliac LN and thus would have downstaged the patient from an initial IIIA to IIA. The patient also received 4 cycles of EBOEP followed by a CR, while the cervical LN remained unchanged.

Another case showing correct downstaging of HL done by PET presented with a similar situation. This patient had an initial manifestation of HL in the cervical and supraclavicular LNs but also showed an abdominal LN. PET would have staged this patient as IIA. Standard CT staging led to stage IIIA disease. After chemotherapy, the abdominal lymph node remained unchanged in this patient, who otherwise had a CR of his disease.

In these six patients we are able to relate the PET results to the subsequent follow-up after therapy, thus proving them to be correct.

In another five patients (18%), additional LN involvement in excess of what had been described using the standard staging was detected by PET. This, however, did not lead to a change in the Ann Arbor classification. In one further case, bone marrow tumor sites were detected by PET (Fig. 2a, b) in a patient with otherwise supradiaphragmal HL IIa according to CT alone but confirmed by bone marrow biopsy.

Using the data of the six patients in whom the follow-up proved the correctness of the imaging results regarding calculation of sensitivity and specificity, the standard staging approach led to a sensitivity of 64% with a specificity of 94% for the detection of affected LNs. In these patients

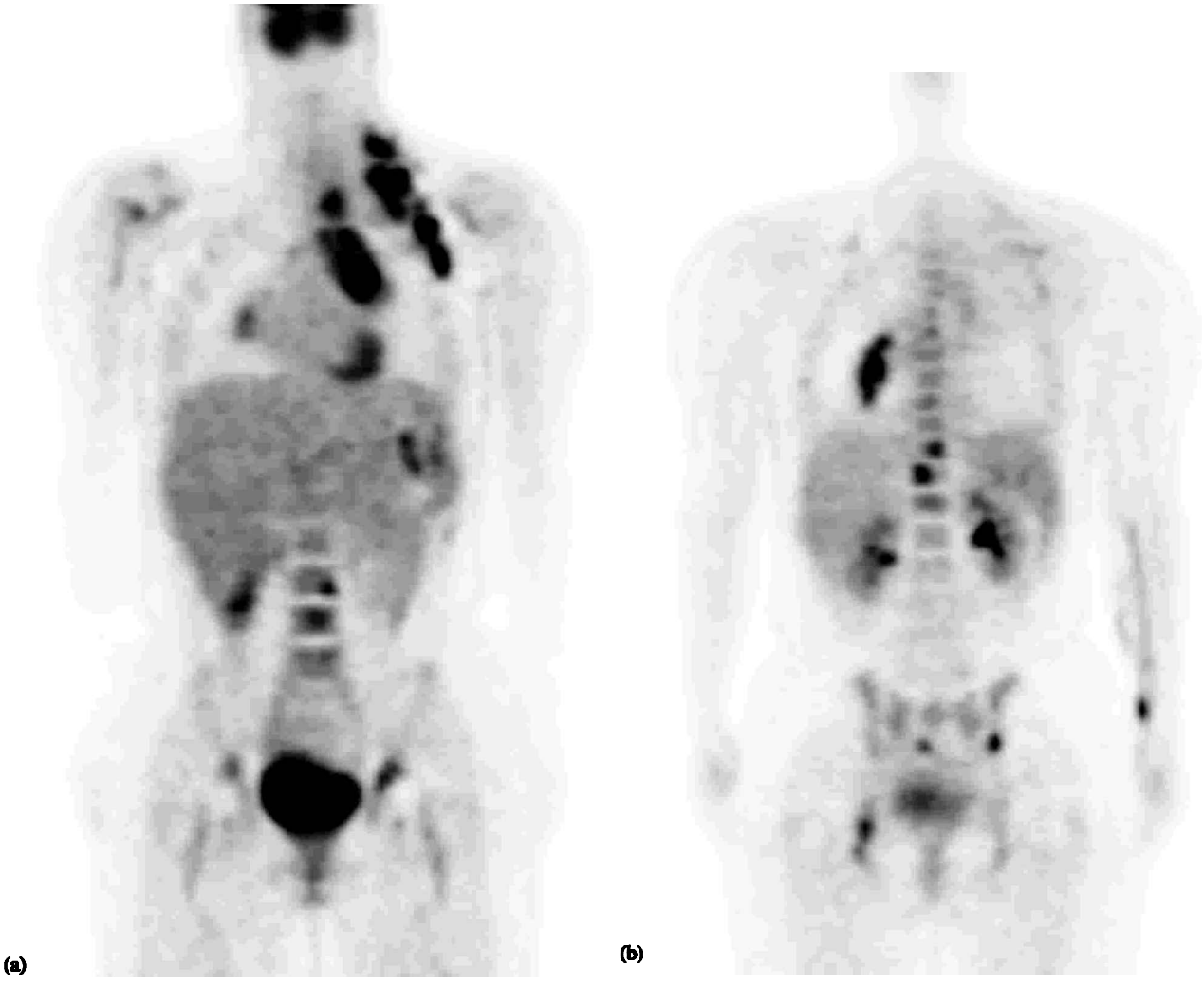

Fig. 2. Supradiaphragmal Hodgkin's lymphoma (HL) with multifocal bone marrow tumor sites. In addition to the nodal status, an excellent overview of the bone marrow tumor sites is given.

the PET scan did not show false-negative or false-positive results.

DISCUSSION

Staging of HL today is done using conventional techniques that evaluate the structure and its anomalies in patients with HL (4). It must, however, be borne in mind that the size and shape are still indirect parameters of LN tumor burden, as there may also be other reasons for LN enlargement. Furthermore, an approach as chosen by radiological methods can have some limitations not only because of normal-sized LN metastases but also as a result of tumor in LN or parenchymal structures that is missed because of low tumor–non-tumor contrast within the tissue or because of partial volume effects in a still mainly axially oriented method such as CT.

Given the advantages—general availability and low cost—of sonography and CT, it is known that these techniques miss a considerable number of tumor sites in both lymph nodes and organs. In a group of 100 HL patients undergoing laparotomy, Munker et al. (4), for example, demonstrated that CT had a low sensitivity of only 37% for detection of splenic and similarly of liver involvement with HL.

Thus PET using FDG has gained increasing acceptance as a non-invasive tool for staging of HL and for its therapy control (5–7). In a large interdisciplinary review, it was summarized that PET was roughly 10% more sensitive than conventional staging at a high specificity of 85–90%. PET also leads to relevant changes in further treatment in about 10% of patients (2). One drawback of earlier studies is the frequent mix of HL patients and those suffering from non-Hodgkin's lymphoma (NHL). To further increase the body of data dealing with the clarified clinical situations, we conducted this study during the initial staging of HL. All of the patients exhibited intense FDG accumulation in LNs and/or organs.

Only histopathological verification of these (and all non-affected) sites would serve as a gold standard. As it is impossible to obtain this gold standard, the only technique that could be used to evaluate the results of conventional staging versus PET would be post-therapeutic follow-up. In our study, PET detected tumor-like glucose consumption in excess to all known sites according to conventional staging in approximately 40% of patients. This changed the staging in more than 20% of these patients. In these patients, the PET results proved to be correct on the basis of the post-therapeutic follow-up. The other patients with discordant results showed mainly additional FDG-positive lesions. There were also three LN regions that were rated as positive by CT because of enlarged LNs that showed no increase in FDG consumption. These findings could not be related to their potentially false-positive or false-negative status.

Overall, our data confirm earlier studies that show a high sensitivity and specificity of PET for the initial staging of HL. Although we observed no false PET results, it is known from the literature that PET yields a risk of false-positive lesions, which might be due to inflammatory processes, and also of false-negative results. A recently published study by Weihrauch et al. demonstrated false-negative PET results in 12% of CT-evaluated positive sites in six patients (3).

Taking the difficulty of the missing gold standard into account, even the remaining approach of a follow-up under therapy remains highly questionable. False-positive/-negative CT or PET sites, e.g. in LNs, will always be affected by therapeutic regimens routinely employing chemotherapy. A drawback of the present study is in using CT findings from different radiological institutions, giving rise to the assumption of a potentially heterogeneous quality in performing and reading the study. This must be taken into account and it might be that high-end, multi-slice CT under experimental conditions leads to better results using this technique. This, however, has no impact on patients being evaluated clinically.

We also did not evaluate the bone marrow findings of PET that was rated as potentially affected by HL in three patients. It is known, that FDG yields false-negative information regarding bone marrow infiltration in approximately 5% of patients and in these cases the HL infiltration was limited to less than 10% of total cellularity (8, 9). In contrast, these studies showed that, even in cases with a negative bone marrow biopsy, bone marrow infiltration can be reliably detected by PET by revealing the site of tumor to be located distant from the site of routine bone marrow biopsy.

In summary, our study extends the evidence that a single FDG-PET during the initial staging of HL can be superior to the actual routine staging protocol. The number of additional tumor sites and the degree of changes in the staging in our study are quite similar to the results of earlier studies (10). There is still some controversy about the role PET should play during the staging of HL. While Hoh et al. (11) proposed a routine staging utilizing PET to be cost effective, other studies (3) denied a role for PET as a routine tool in this indication.

Nevertheless, we would consider PET to be the method of choice during the initial staging of HL. It remains to be demonstrated in a larger number of patients investigated on a routine clinical basis whether PET will finally prove to be cost effective during a routine application or whether it should be confined to selected patients only.

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