PET Scan for HL Restaging

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2.1 Introduction

Hodgkin lymphoma is relatively rare disease, with an annual incidence of 3 per 100,000. The peak incidence is in the early adulthood and in the elderly. Patients most commonly present with lymphadenopathy in the cervical region and the mediastinum. The mediastinal region often shows bulky disease. When more regions are involved, the areas are usually contiguous, consistent with the view that spread is predominantly through the lymphatic channels [1]. Accurate staging and restaging provide important prognostic information and dictate the appropriate treatment strategy. With the introduction of FDG-PET and later on of FDG-PET/CT during the last decennia, the accuracy of staging and restaging has improved enormously [2, 3].

The widely used International Working Group criteria for response assessment of lymphoma, published in 1999, were based predominantly on CT and did not include PET as part of response assessment [4]. The term "complete remission unconfirmed" (CRu) was originally coined to describe persistence of a residual mass post-therapy, with resolution of all clinical symptoms. Patients with Hodgkin lymphoma often present with a bulky mediastinal mass, while after treatment fibrotic residual tissue can be observed. An optimal treatment strategy for patients with HL combines high cure rates with minimal toxicity. The correct identification of patients with a complete remission, with or without large residual masses, reduces the number of patients exposed to unnecessary toxicity. With the introduction of FDG, the ability to distinguish between viable tumor and necrosis or fibrosis became available [5]. In one study, it was observed that that the majority of the CRu patients had negative FDG-PET findings with progression-free survival rates equivalent with CR patients [6]. Hence, FDG-PET may be useful in finding the balance between a highly effective treatment and minimal toxicity. Considering the more widespread use of FDG-PET in response assessment of lymphoma, it became clear that the International Working Group criteria warranted revision. For this purpose, in 2007 the Competence Network Malignant Lymphoma convened an International Harmonization Project with five subcommittees among which the imaging subcommittee. The aim was to develop guidelines for performing and interpreting FDG-PET for treatment assessment in lymphoma, to ensure the reliability of the method, both in the context of clinical trials and in clinical practice. Since the publication of the revised Cheson criteria for staging and restaging in malignant lymphoma [7, 8], PET has

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become a mandatory and essential diagnostic technique in evaluation treatment response. Since that time, many reports have shown the value of PET imaging of Hodgkin lymphoma for evaluation response assessment after chemotherapy or radiotherapy [9–15]. However, with increasingly sensitive and specific technologies for disease assessment by the introduction of new PET/CT imaging, a modernization of the response criteria became necessary. In 2014, the Lugano classification has been published, aiming to improve the evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials [16, 17]. This chapter will summarize the use of FDG-PET/CT for response evaluation after therapy and discuss the some technical considerations and pitfalls that may influence correct assessment of PET/CT. Also standardization of the interpretation of criteria and semiquantitative evaluation are being described.

2.2 Relevance of Response Monitoring

As Hodgkin lymphoma is generally a curable disease, the goal of treatment is to achieve a complete remission (CR), which is a prerequisite for cure. Accurate remission assessment after the completion of therapy is therefore essential to detect patients with incomplete response, to improve the prognosis of those patients by timely introduction of more effective treatment options. However, also overtreatment must be prevented to avoid treatment-related toxicity. As Hodgkin lymphoma patients often present with bulky lymphadenopathy, it is well know that many patients have (minor) lymphadenopathy after therapy. Particularly for response assessment at therapy conclusion, FDG-PET has been shown to be considerably more accurate than CT because of its ability to distinguish between viable tumor and necrosis or fibrosis in post-therapy residual masses that are frequently present in patients with Hodgkin lymphoma without any other clinical or biochemical evidence of disease [3]. Its routine use has been recommended to assess the post-therapy response of HL, especially if CT reveals a residual mass.

2.3 Evaluation After First-Line Therapy

During the last 20 years, many retrospective and prospective studies have been published on the value of FDG-PET and PET/CT response assessment at conclusion of therapy [9–15].

Two systematic reviews have analyzed the diagnostic accuracy of FDG-PET for posttreatment evaluation of Hodgkin lymphoma patients after first-line chemotherapy [18, 19]. Although there is a major methodological variability between the studies included in both reviews, these studies consistently show that FDG-PET has a high specificity in this setting for a pooled sensitivity (vs. the gold standard of tumor-positive biopsy/clinical follow-up of at least 1 year) of 84 % for Hodgkin lymphoma (see Table 2.1). The negative predictive value (NPV) for FDG-PET in post-therapy evaluation of HL appeared to be very high, ranging from 71 to 100 %. However, the positive predictive value (PPV) exhibits a wider range (13–100 %) with a weighted average of 62 %. Possible explanations for this relatively low PPV are the substantial fraction of HL patients that received radiation therapy prior to undergoing FDG-PET, resulting in frequent occurrence of false-positive post-radiation inflammatory changes and the more frequent

Table 2.1 Several studies have investigated the Positive Predictive value (PPV) and Negative Predictive value (NPV), illustrating the high NPV and variable PPV

Study and year	% PET positive	% PET negative	PPV (%)	NPV (%)
Filmont, 2004	44	56	78	100
Friedberg, 2004	25	75	50	96
Guay, 2003	25	75	92	92
Jerusalem, 1999, 2003	13	87	100	92
Kobe, 2008	26	74	–[a]	94
Mikosch, 2003	61	39	89	100
Mocikova, 2004	32	68	13	100
Rigacci, 2005	29	71	50	100
Schaefer, 2004	22	78	100	71
Spaepen, 2001	8	92	100	91
Wickmann, 2003	52	48	60	91

Modified from Juweid, *JNM*, [40]

[a]PET-positive patients received radiotherapy

occurrence of thymic hyperplasia in the generally younger HL patients, which can also lead to a false-positive interpretation of posttreatment PET scans. Hence, radiotherapy may hamper the interpretation of posttreatment PET scans. Recently, Morbelli et al [20] demonstrated that previous radiotherapy was the most important predictor of false-positive FDG-PET performed in asymptomatic lymphoma patients in remission. With a positive PET scan rate of about 30 % and a PPV of 62 %, misclassification of disease status due to a positive post-therapy PET affects approximately 11 % of all patients. If further treatment based on residual metabolically active disease on PET/CT is being considered, either biopsy or follow-up scan is advised. On the other hand, a 70 % frequency of negative PET combined with a NPV of 94 % translates into a misclassification of only 4 % of all patients. Even in case of a large residual mass, a biopsy is not advised [21].

Alternatively, a CT scan may offer additional information in the posttreatment evaluation of HL. Assessment of tumor size reduction on CT has been studied by Kobe et al. in their HD15 trial in advanced HL. In the subgroup of the 54 PET-positive patients with a relative reduction of less than 40 % on CT, the risk of progression or relapse within the first year was 23.1 %, compared with 5.3 % for patients with a larger reduction. So patients with HL who have PET-positive residual disease after chemotherapy and poor tumor shrinkage are at higher risk of progression or relapse [22]. Hence, a diagnostic CT scan, performed with intravenous and oral contrast agents, should also be performed.

2.4 Evaluation After Second-Line Therapy, Before Autologous Stem Cell Transplantation

For relapsed HL, reinduction chemotherapy and autologous stem cell transplantation can yield a 5-year event-free survival up to 50 % [23, 24]. However, the success of this highly toxic treatment relies on tumor chemosensitivity. Various studies [25–27] have reported that PET/CT using FDG is prognostic in patients with relapsed or refractory HL after salvage chemotherapy before high-dose chemotherapy and autologous stem cell transplantation (ASCT) and is superior to CT alone. Three-year progression-free survival (PFS) and event-free survival (EFS) rates of 31–41 % have been reported for patients with PET-positive scans, compared with 75–82 % for patients with PET-negative scans. A meta-analysis also demonstrated a strong correlation between pre-ASCT FDG-PET results and the outcome after ASCT. A negative pre-ASCT PET not only indicated a longer PFS but also a significant gain in overall survival [28].

2.5 Visual Versus Semi-quantitative Assessment of PET/CT

Visual assessment alone appears to be adequate for determining whether PET is positive or negative at the conclusion of therapy, and quantitative or semi-quantitative approaches (e.g., using the standardized uptake value [SUV]) do not seem necessary for daily practice use. In the Lugano classification, the 5-point scale (5-PS) or Deauville score is recommended (see Table 2.2) [17]. The 5-PS was intended as a simple, reproducible scoring method, with the flexibility to change the threshold between good or poor response according to the clinical context and/or treatment strategy. The 5-PS has been validated for use at interim response assessment and was adopted as the preferred reporting method at the First International Workshop on PET in

Table 2.2 Deauville score or 5-point score for grading FDG-uptake

The *5-point score* scores the most intense uptake in a site of initial disease, if present, as follows:
1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions
X. New areas of uptake unlikely to be related to lymphoma

Lymphoma in Deauville, France (i.e., Deauville criteria), and in several international trials. At the end of treatment, residual metabolic disease with a score of 4 or 5 represents treatment failure even if uptake has reduced from baseline [16]. A score of 4 or 5 with intensity that does not change or even increases from baseline and/or new foci compatible with lymphoma represents treatment failure at the end-of-treatment assessment. However, validation of DS for end-of-treatment assessment has only been published for primary mediastinal B-cell lymphoma (PMBCL) which has similarities with mediastinal bulky HL [29].

Metabolic changes measured by standard uptake values are continuous, reflecting an in vivo therapy response scale. However, SUV measurements heavily depend on several factors related to PET protocols, e.g., interval between injection and scanning, blood glucose concentrations, body weight, and individual scanner-dependent features [30]. The variability of SUV values decreases the potential accuracy of absolute cutoff values. Hence, in daily practice, visual assessment of posttreatment PET in HL is preferred above a semiquantitative approach.

However, not only the correct scoring of the FDG avidity compared to the mediastinum and liver is important, the most relevant issue is the interpretation of these images in the clinical context. For experienced nuclear medicine physicians, the recognition of specific patterns in FDG uptake is essential [31, 32].

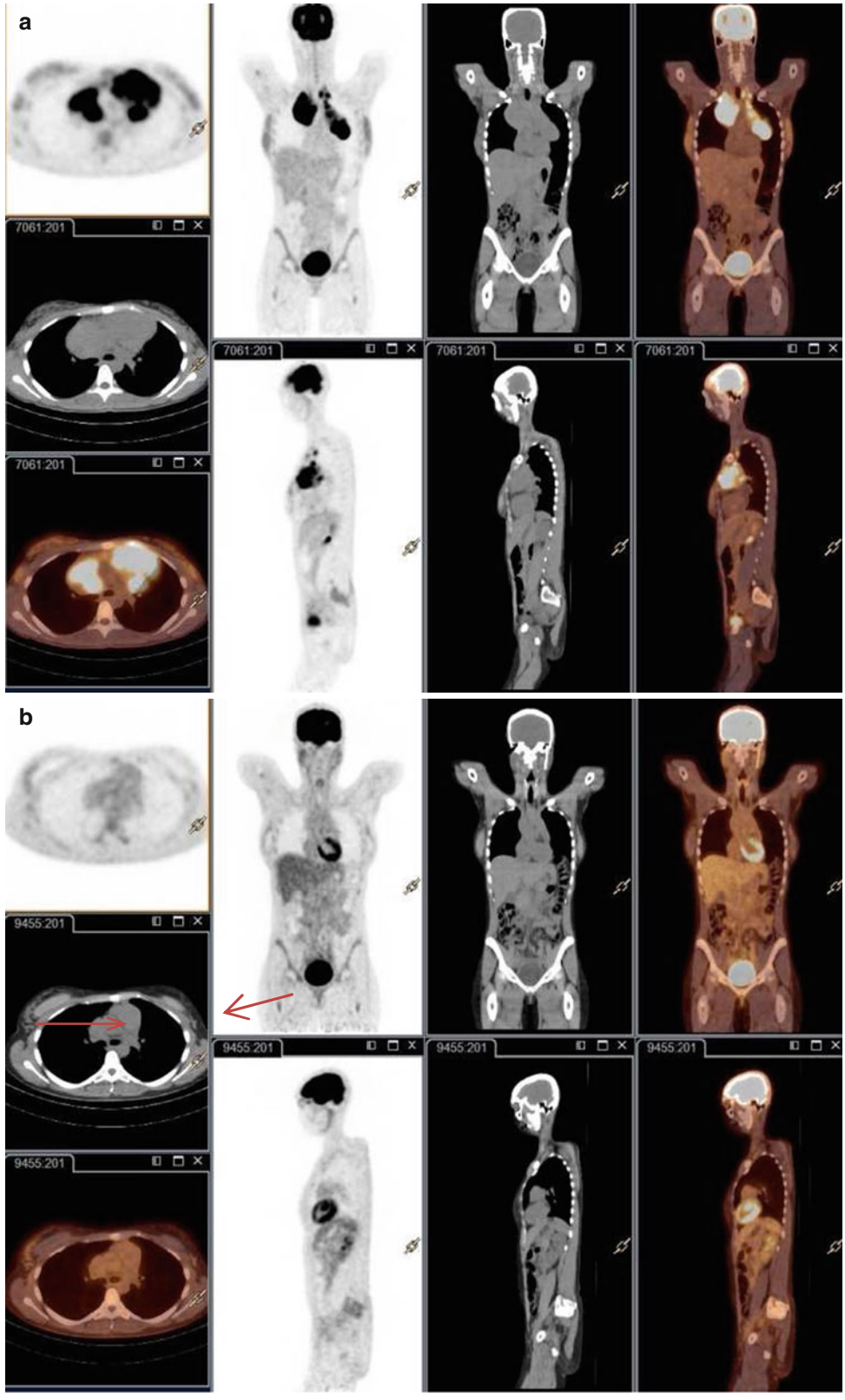
Most common causes of false-positive FDG-PET results in treatment evaluation are pneumonia and other infections (induced by neutropenic periods after chemotherapy), sarcoidosis and sarcoid-like reactions, inflammatory lung processes, brown fat uptake, second primary malignancies, radiotherapy-induced pneumonitis, and thymus hyperplasia (especially in children and young adults) [33–36]. Thymic hyperplasia is a common phenomenon that occurs after completion of treatment. It has been proposed that this finding is due to an immunologic rebound characterized by thymic aplasia followed by hyperplasia [37]. For illustrations see Figs. 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, and 2.7.

In some cases, uncertainty will exist, and discussion concerning true positive PET lesions (i.e., persisting Hodgkin activity) or false-positive PET lesions (i.e., inflammation following treatment) cannot be resolved. In such clinical situations, an often invasive biopsy procedure is the only solution to bring clarity. If such a surgical intervention is not feasible, the alternative option can be to perform a PET/CT scan after 2–3 months. Recently we have treated a young man with relapsed Hodgkin lymphoma, with nodal involvement in the axillary lymph nodes, just outside the radiation field. His original disease was located in the cervical and mediastinal region. During second-line treatment with DHAP and brentuximab vedotin (clinical trial Phase II), his axillary lymph nodes disappeared, but a new lesion came up in the mediastinal area. Discussion about the origin of this new lesion could not be settled. We have asked the thoracic surgeon to perform a mediastinotomy and remove the PET-positive lesion. It appeared to be fibrotic tissue with sheets of active macrophage involvement and debris. He remained in complete remission after autologous stem cell transplantation.

2.6 Technical Considerations

Although never studied in detail, it might be expected that assessment of PET/CT for post-treatment evaluation in HL is more accurate than assessment of PET "stand-alone" imaging results. Especially for the proper evaluation of FDG uptake in the mediastinal region, a secure correlation with anatomical structures is essential.

Fig. 2.1 (**a**) A 35-year-old female with biopsy-proven Hodgkin's disease; the figure represents the initial FDG-PET/CT scan, which was used for staging. The findings are consistent with bulky mediastinal nodal Hodgkin's lymphoma. (**b**) FDG-PET/CT restaging after chemotherapy (BEACOPP escalated). The post-therapy scan shows a residual mediastinal mass on the CT images (*red arrow*). The FDG uptake was low reflecting an uptake intensity of 2 of the 5-point scale (5-PS), consistent with a complete metabolic response with a residual mass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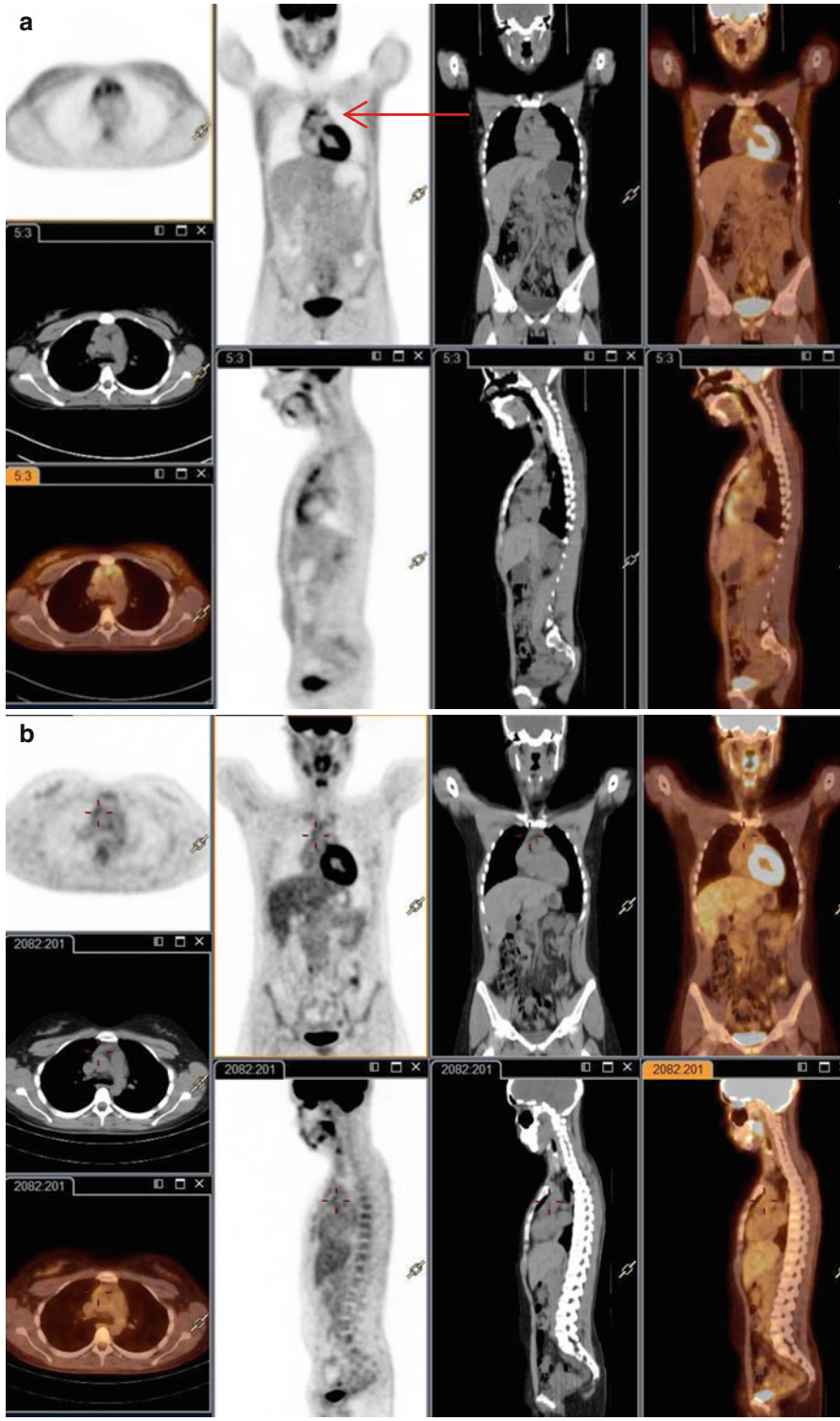

Fig. 2.2 (**a**) Follow-up FDG-PET scan in 22-year-old patient with HL, located in mediastinum and cervical lymph nodes. The posttreatment PET scan shows increased uptake in the mediastinal area (tracer uptake intensity 4 of the 5-PS); however, pattern and intensity of the FDG uptake are consistent with thymic FDG uptake in a young adolescent. (**b**) A PET scan performed 4 months later during follow-up demonstrated a spontaneous regression of rebound uptake in thymus. This observation was consistent with the clinical course showing no relapse of HL in this patient. *Red arrow* pointing to the mediastinal FDG uptake

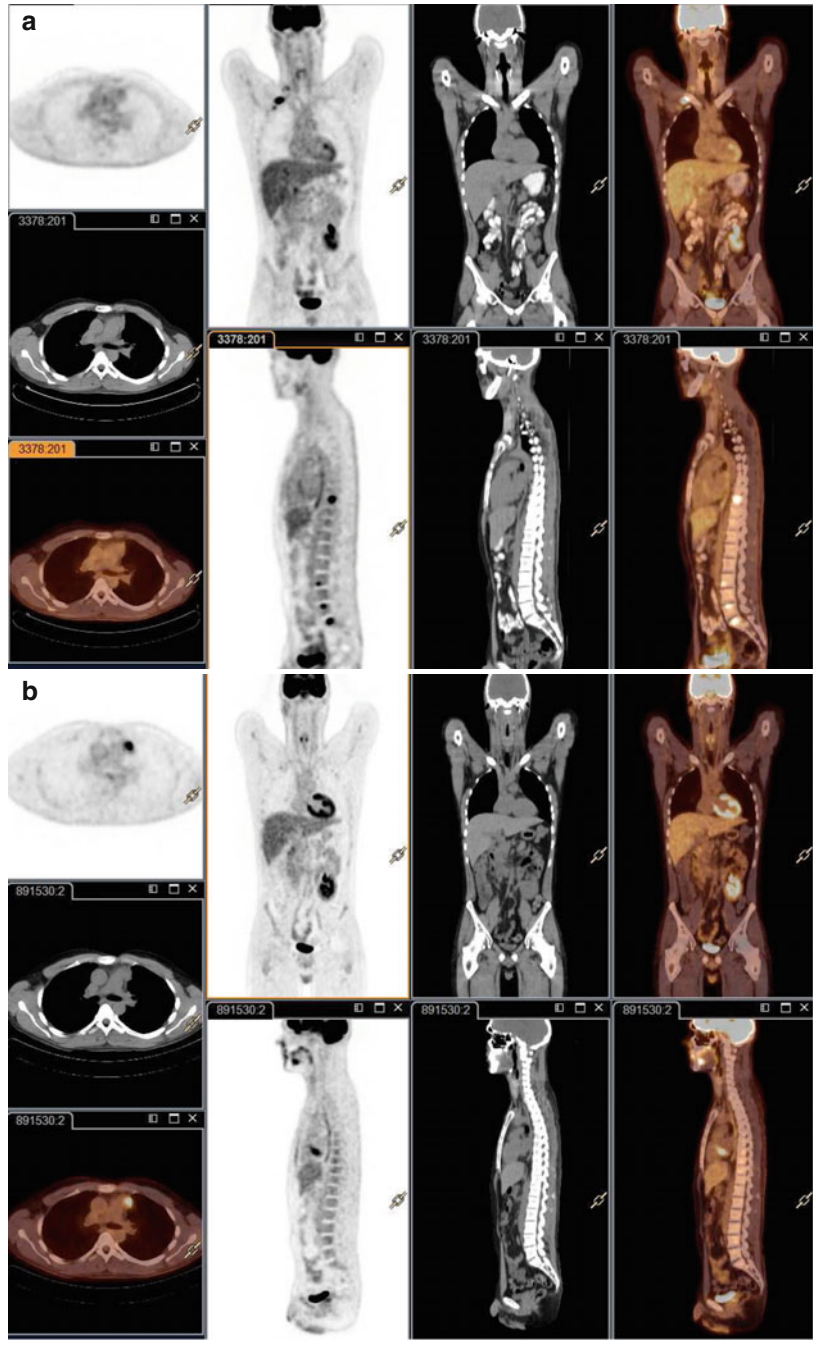

Fig. 2.3 (**a**) A 23-year-old patient with initial bulky mediastinal HL (stage IV); patient was treated with BEACOPP chemotherapy and mediastinal radiotherapy. After this initial treatment schedule, a FDG-PET scan showed a relapsed HL with nodal infraclavicular disease and extra-nodal localization in the spine. (**b**) After treatment with DHAP chemotherapy, the PET/CT scan demonstrated a good treatment response with no FDG uptake in the infraclavicular nodal region and in the extra-nodal vertebral localizations (see coronal and sagittal views). However, this PET scan showed intense uptake in the mediastinal region (transaxial PET image **b**). This nodal uptake was not visible on the pretreatment scan at relapse (see axial image **a**). Therefore, a biopsy was performed. The biopsy of the mediastinal node with increased FDG uptake revealed the presence of macrophages and lymphocytes in a lymph node. Hence, this mediastinal FDG uptake reflected a false-positive lesion with a local inflammatory response

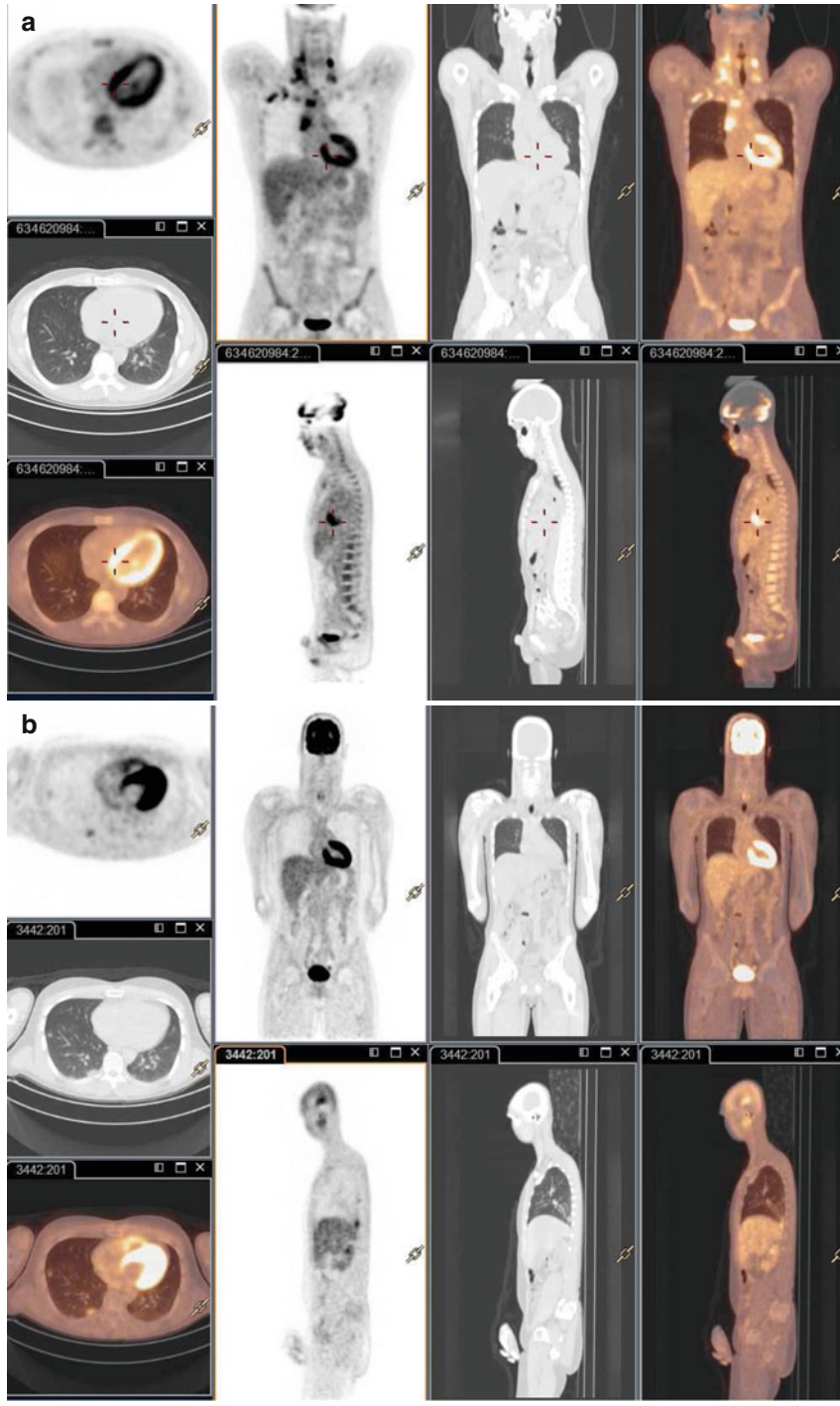

Fig. 2.4 (**a**) Baseline FDG-PET/CT in staging HL with intense FDG uptake in nodular disease in the cervical regions, mediastinum, and right axilla. (**b**) FDG-PET/CT after chemotherapy. The PET scan showed disappearance of the FDG uptake in the initial nodal localizations reflecting a complete metabolic response; however, two sites with FDG uptake were seen in the right lung (axial image). The lung uptake was new compared to the baseline PET scan (compare axial images **a** and **b**); therefore, the pulmonary lesions were classified as a category X of the 5-PS ("new areas of uptake unlikely to be related to lymphoma") representing inflammatory parenchymal lung uptake (infection)

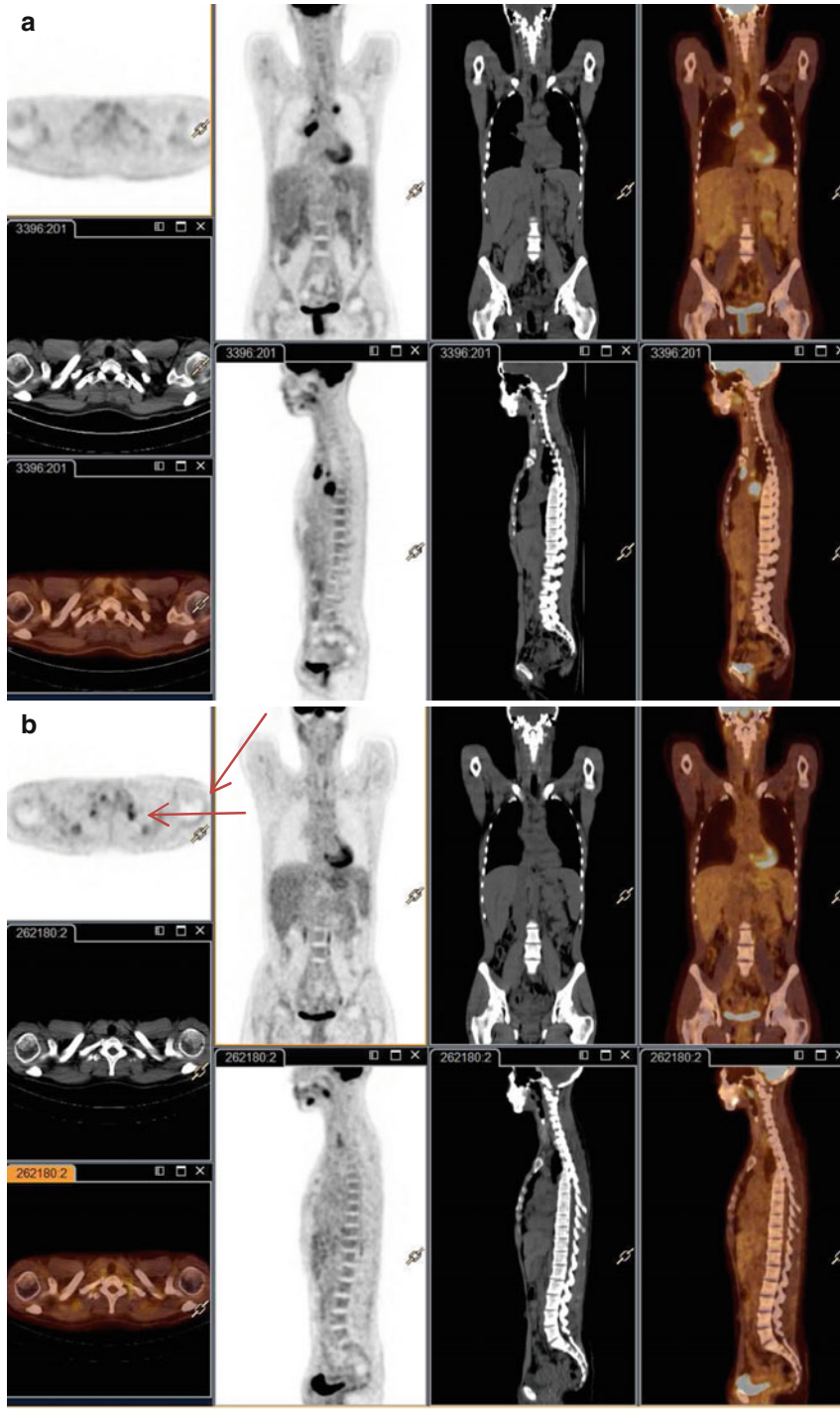

Fig. 2.5 (**a**) FDG-PET/CT staging of HL patient with nodal mediastinal disease (see coronal and sagittal images). (**b**) The posttreatment PET/CT after ABVD showed a complete metabolic response (compare coronal and sagittal images of **a** and **b**); however, symmetric cervical FDG uptake was seen (*arrow*, axial images **b**). These cervical localizations were new compared to the baseline PET scan (axial image **a**). Correlation with the CT images demonstrated no nodal FDG uptake, but FDG uptake in fat, consistent with symmetric brown fat uptake. Altogether, the cervical uptake was classified as an X classification of the 5-PS. *Red arrow* pointing to the cervical FDG uptake

Using PET/CT instead of PET and separate CT facilitates a more accurate assessment.

In the current Lugano criteria, a staging PET/CT is not only advised but mandatory for a good posttreatment evaluation [17].

2.7 Practical Considerations

For ordering physicians, it is important that they understand the clinical information needed by imaging physicians to optimize the interpretation of such studies. The request for the PET/CT examination should include sufficient medical information to demonstrate medical necessity and should at least include the diagnosis and questions to be answered. For posttreatment evaluation, it is essential that recent infections, comorbidity, and diabetes mellitus are mentioned. The results of prior imaging studies should be available to review, including planar radiography, CT, and staging FDG-PET/CT. An overview of used medication, especially antidiabetic medication, corticosteroids, and growth factors and in the case of therapy evaluation type and date of last chemotherapy or radiotherapy must be mentioned [30].

The timing for end-of-treatment evaluation PET should be at least 3 weeks after chemotherapy [8] and preferably 8–12 weeks after completion of radiotherapy. This approach should be adopted to improve diagnostic accuracy by avoiding post-therapy inflammatory changes.

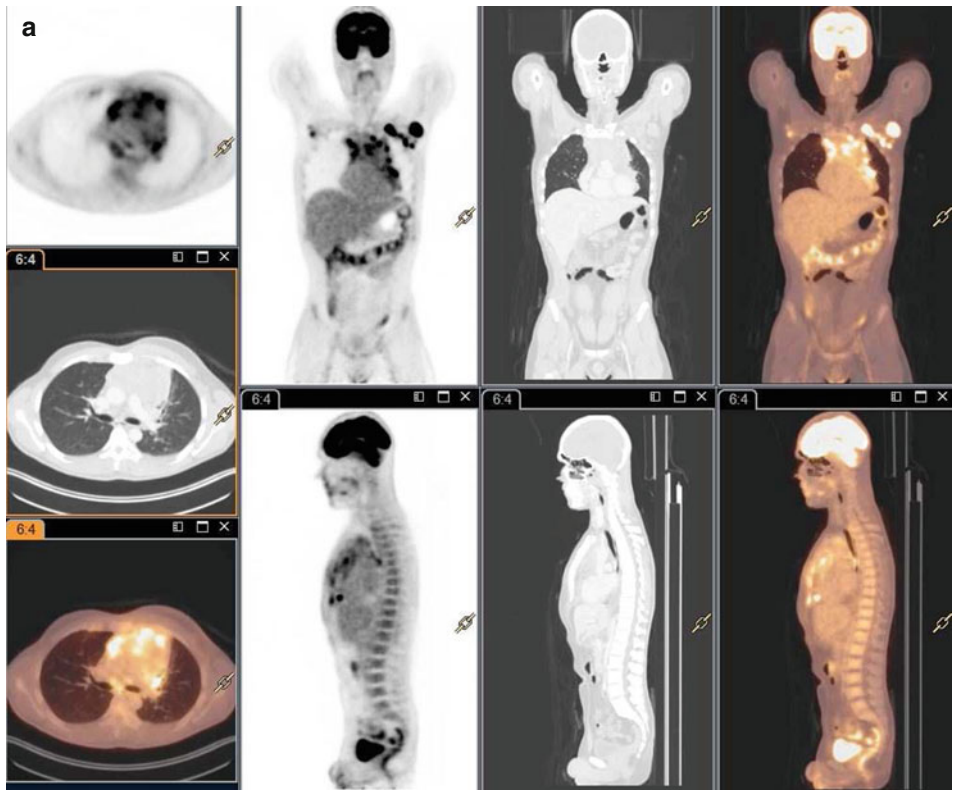

Fig. 2.6 (**a**) FDG-PET/CT scan of patient with a relapsed HL; images show intense uptake in the mediastinal and axillary lymph nodes. The FDG uptake in the bowel has a diffuse pattern and does not reflect HL. (**b**) A posttreatment FDG-PET scan showed a good treatment response. However, the PET images revealed a new focus with intense FDG uptake in the left lung (PET classification: left lung focus, category X, inflammatory FDG uptake due to pulmonal infection). (**c**) During follow-up, the pulmonary infection was treated with antibiotics, and the FDG-PET scan showed a regression of the pulmonary infection. However, this end-of-treatment PET scan showed increased uptake in the left axillary region (intensity 4 on the 5-PS), reflecting a partial remission of HL

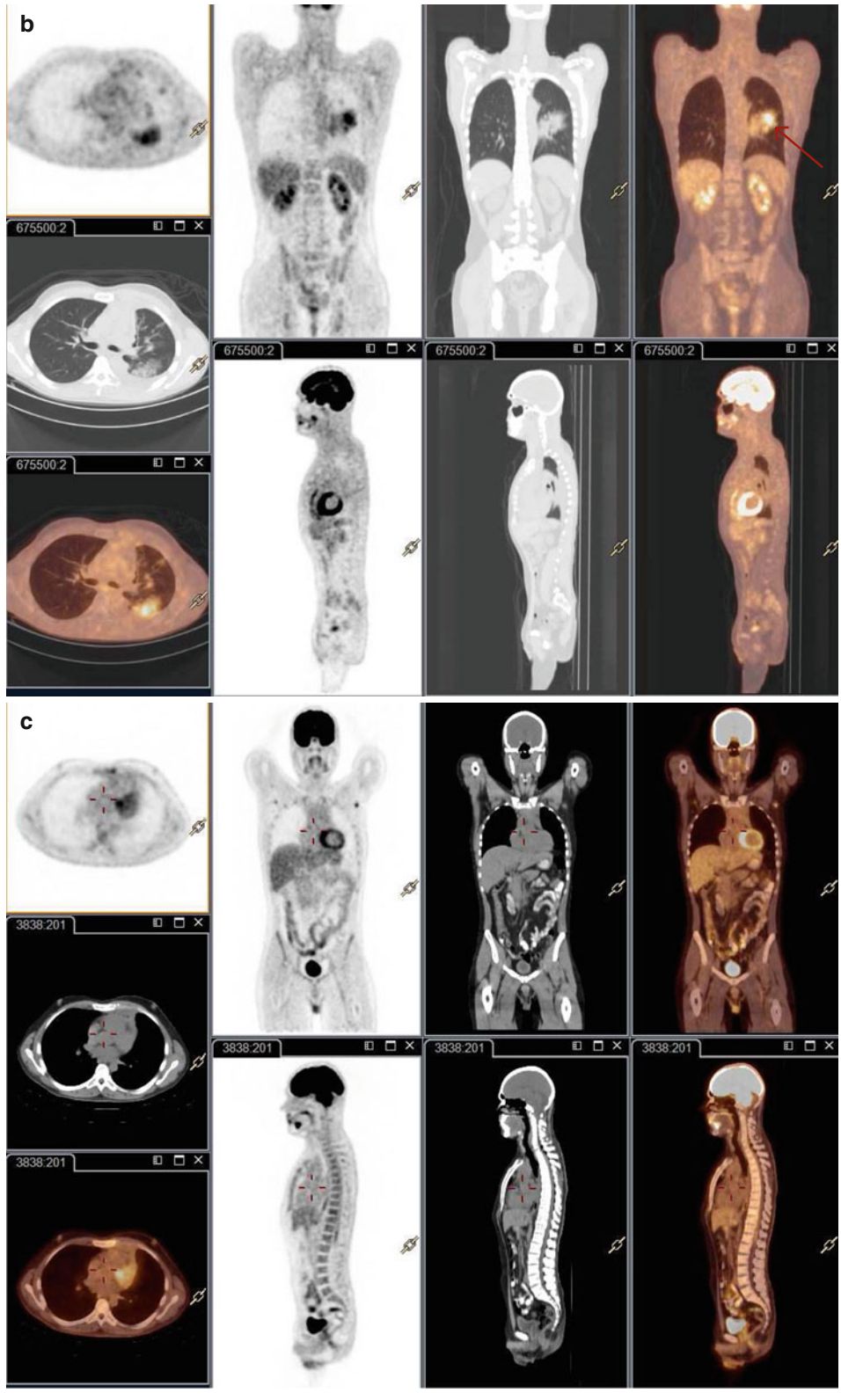

Fig. 2.6 (continued)

2.8 PET-Guided Radiotherapy as Consolidation Treatment Following Chemotherapy

By using PET/CT for response assessment after chemotherapy, the use of radiotherapy as consolidation has greatly diminished. In former days, most patients with residual tissue on CT after chemotherapy received adjuvant radiotherapy. However, with the introduction of PET/CT, it is known that even for patients with large residual masses, but without FDG avidity, there is no need for radiotherapy. The negative predictive value (NPV) of FDG-PET has been investigated by the German Hodgkin Study Group in the HD15 trial. In this trial, patients with advanced stage HL were treated with 6 or 8 cycles of BEACOPP. The NPV appeared to be 94 % after a follow-up of 12 months. Thus, following BEACOPP consolidation radiotherapy can be omitted in PET(−) patients with residual disease without increasing the risk for progression or early relapse compared with patients in complete remission [38, 39]. In this trial, only 11 % of patients appeared to be PET(+) and received additional radiotherapy. For advanced stage HL patients treated with ABVD, PET-guided radiotherapy has not been validated. However, there are no arguments to doubt on the relevance of PET-guided radiotherapy in this setting.

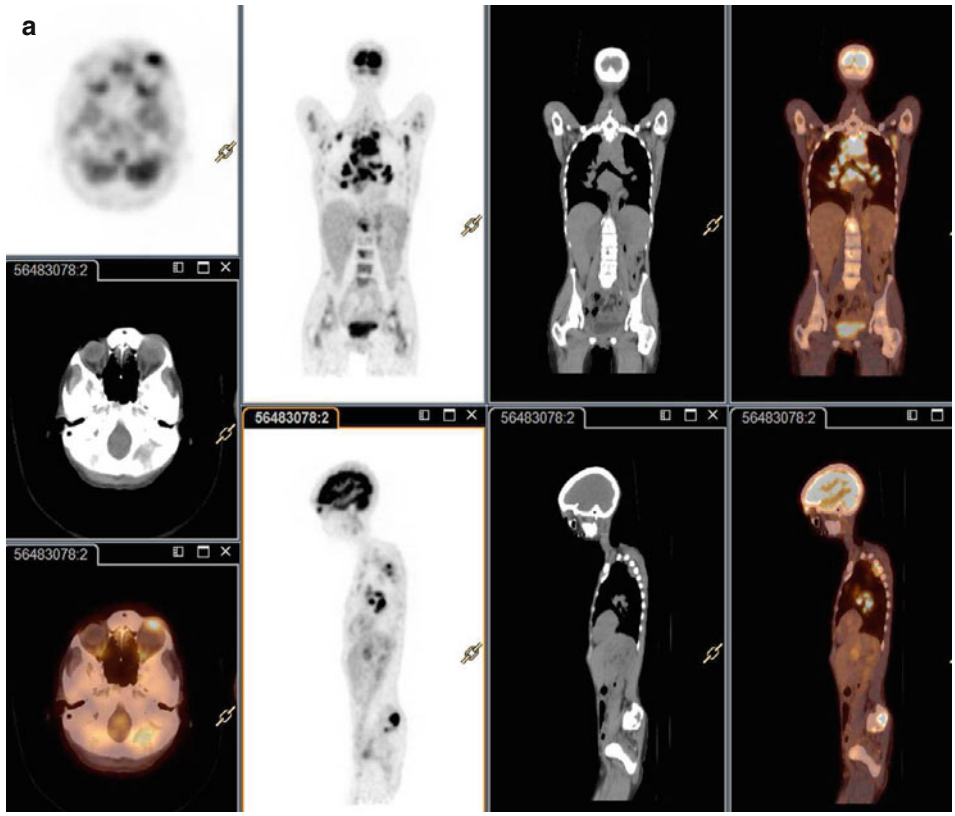

Fig. 2.7 (**a**) Patient with known sarcoidosis in the mediastinum and hilar lymph nodes, presented with a localization of Hodgkin lymphoma in left orbital region (rare localization, biopsy proven); see axial image. FDG-PET demonstrating intense FDG uptake in orbital region, mediastinal and hilar FDG uptake, and ossal foci. (**b**) Posttreatment FDG-PET showing regression of the orbital lesion and the bone marrow localizations (see axial and sagittal images). However, mediastinal and hilar FDG uptake remains abnormal with multiple focal areas with increased FDG uptake. This uptake may reflect sarcoidosis or a partial response. (**c**) During follow-up an additional FDG-PET scan was performed. During follow-up the biopsy-proven HL site in the orbita remained without any sign of relapse. The mediastinal and hilar FDG uptake showed some decline of FDG uptake, consistent with a decline of sarcoidosis activity. During 2 years of follow-up, no relapse of HL was observed

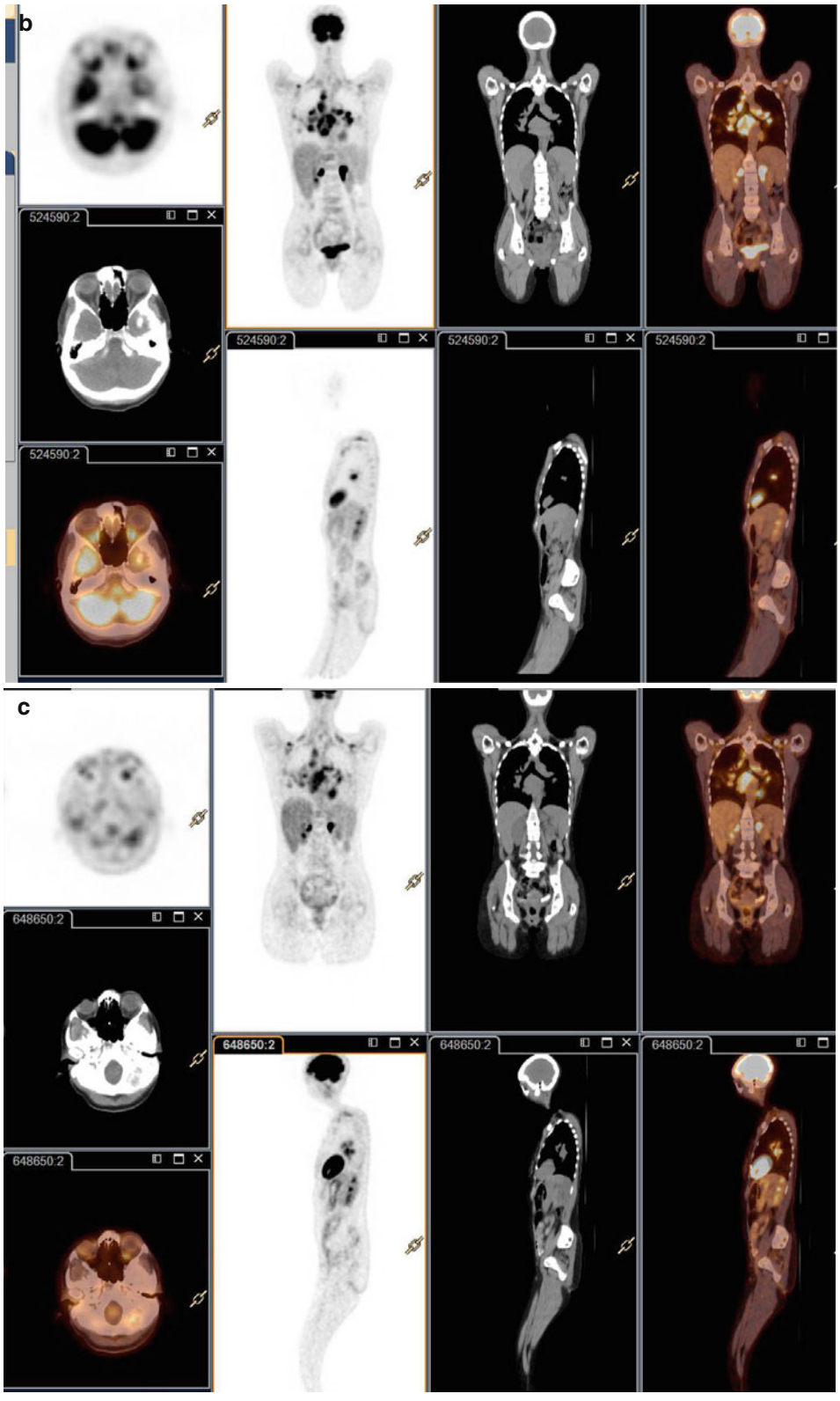

Fig. 2.7 (continued)

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