Hodgkin Disease: Diagnostic Value of FDG PET/CT after First-Line Therapy—Is Biopsy of FDG-avid Lesions Still Needed?[1]

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Purpose: To retrospectively determine the sensitivity and specificity of co-registered fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in patients with Hodgkin lymphoma after first-line therapy, with use of clinical follow-up or biopsy results as the reference standard.

Materials and Methods: Informed consent was obtained for imaging and included consent to use patient data for research purposes. Institutional review board approval was obtained. Between May 2001 and July 2005, the data for all patients ($n = 66$) at the authors' institution with proved Hodgkin lymphoma after first-line therapy were retrospectively reviewed. PET/CT scans were evaluated for the presence of abnormal FDG uptake and residual masses after the end of treatment and at further follow-up. All patients with pathologic FDG lesions underwent surgical biopsy for histopathologic confirmation. All patients with negative PET/CT scans at follow-up were evaluated for disease-free survival.

Results: An FDG-avid lesion was detected at PET/CT in 27 of the 66 patients (mean age ± standard deviation, 33.0 years ± 12.2). Recurrence of Hodgkin lymphoma was confirmed with biopsy in 23 of the 27 patients. The mean maximum standardized uptake value (SUV) of the histopathologically proved lesions was 7.32 (±2.01). Four patients had false-positive findings at PET/CT: Biopsy revealed only inflammatory changes, and the mean maximum SUV was 7.30 (±2.53). Thirty-nine patients (mean age, 36.7 years ± 10.8) did not have FDG-avid lesions and remained free of disease after a mean clinical follow-up of 26.2 months (±12.5) (specificity, 91% [39 of 43 patients]; sensitivity, 100% [23 of 23 patients]). The presence of bulky disease (>5 cm) after the end of treatment was a significant predictor of recurrent disease ($P < .05$).

Conclusion: The authors conclude that FDG PET/CT can help exclude persistent and/or recurrent Hodgkin lymphoma after first-line therapy. Because of the false-positive results and the toxicity of salvage chemotherapy, including high-dose chemotherapy with autologous stem cell support, biopsy of the FDG-avid lesion is still needed.

Supplemental material:
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Radiology

Positron emission tomography (PET) with fluorine 18 fluorodeoxyglucose (FDG) is used for staging and follow-up examinations in patients with Hodgkin lymphoma (1,2). Previous studies have revealed that FDG PET has high sensitivity and specificity with regard to staging and restaging in patients with Hodgkin lymphoma. With the introduction of in-line PET/computed tomographic (CT) scanners, a combined method of metabolic and morphologic imaging is available because PET and CT data can be acquired during the same imaging session (3). At our institution, low-dose CT without the intravenous injection of iodinated contrast material is routinely used for attenuation correction and image co-registration. Previous studies have revealed that imaging with low-dose nonintravenous contrast material–enhanced CT alone might be sufficient for staging and restaging in patients with Hodgkin lymphoma or aggressive non-Hodgkin lymphoma (4). These results, however, were not verified with histopathologic examination, and the exact clinical value of FDG PET/CT remains unclear. To our knowledge, until now investigators in no study had examined patients with Hodgkin lymphoma who were suspected of having recurrent disease after first-line therapy.

Thus, the aim of our study was to retrospectively determine the sensitivity and specificity of co-registered FDG PET/CT in patients with Hodgkin lymphoma after first-line therapy, with use of clinical follow-up or biopsy results as the reference standard.

Materials and Methods

Patients

Signed written informed consent was obtained for imaging and included consent to use patient data for research purposes. Our study had institutional review board approval.

All patients with histopathologically proved Hodgkin lymphoma evaluated and treated at our institution after first-line therapy were consecutively included in this study (n = 66; 46 male, 20 female; age range, 11–76 years; mean age ± standard deviation, 35.2 years ± 11.7). No patients were excluded from this cohort. All PET/CT examinations were performed between May 2001 and July 2005. All patients underwent PET/CT to monitor disease in the follow-up period after first-line therapy. In 58 patients, the initial FDG PET/CT examination was performed within 2 months after the end of therapy and at a time point after that as requested by the oncologist. Eight patients suspected of having recurrent disease were referred to our tertiary care institution after first-line treatment and had undergone only PET/CT for the detection of recurrent disease. No second-line or other therapy was performed previously in these patients.

In all patients with pathologic FDG-avid lesions at PET/CT after first-line therapy (n = 27; mean age, 33.0 years ± 12.2), surgical biopsy was performed for histopathologic confirmation of the FDG-avid lesions. All patients with negative findings at follow-up PET/CT (n = 39; mean age, 36.7 years ± 10.8) were examined for disease-free survival over a mean of 26.2 months (±12.5).

Treatment

First-line treatment consisted of chemotherapy alone for patients with advanced disease (stage III or IV) or combined-modality treatment for patients with an earlier disease stage (stage I or II). All patients with FDG-avid lesions at PET/CT underwent surgery for biopsy of the FDG-avid lesion and histopathologic confirmation of recurrence. All patients without clinical or imaging findings of recurrence were seen on a quarterly basis in our oncology unit and were examined for disease-free survival (C.T., with 8 years of oncology experience).

Imaging

All data were acquired with a combined PET/CT in-line system (Discovery LS; GE Medical Systems, Waukesha, Wis). In this dedicated system, a PET scanner (Advance NXi; GE Medical Systems) is integrated with a multisection helical CT unit (LightSpeed Plus; GE Medical Systems) and enables the acquisition of co-registered CT and PET images in one session.

Patients fasted for at least 4 hours before undergoing scanning, which started 40–60 minutes after the injection of a standard dose of 370 MBq of FDG. In addition, oral CT contrast material (barium sulfate suspension, Micropaque Scanner; Guerbet, Aulnay-sous-bois, France) was given starting 15 minutes before the injection of FDG. Patients were examined in the supine position. No intravenous contrast material was given for CT scanning. CT scans were initially acquired starting at the level of the head by using the following parameters: 80 mA, 140 kV, 0.5 second per tube rotation, section thickness of 4.25 mm, scan length of 867 mm, and data acquisition time of 22.5 seconds. The

Advances in Knowledge

- FDG PET/CT helped exclude persistent and/or recurrent Hodgkin lymphoma after first-line therapy.
- FDG PET/CT may yield false-positive results after first-line therapy, compared with biopsy.

Implication for Patient Care

- Because of the false-positive results and the toxicity of salvage chemotherapy, including high-dose chemotherapy with autologous stem cell support, biopsy of the FDG-avid lesion is still needed.

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Abbreviations:
FDG = fluorine 18 fluorodeoxyglucose
SUV = standardized uptake value

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CT scan was acquired in a breath hold during expiration and covered the region from the head to the pelvic floor.

Immediately after the CT scan acquisition, a PET scan was acquired by using an acquisition time of 3 minutes for the emission scan per cradle position with a one-section overlap. Six cradle positions from the pelvic floor to the head resulted in an acquisition time of approximately 18 minutes. The CT data were used for attenuation correction, and images were reconstructed by using a standard iterative algorithm (ordered subset expectation maximization). The acquired images were viewed with software that provided multiplanar reformatted images of PET, CT, and fused data with linked cursors (Xeleris workstation, version 1.0728; GE Medical Systems).

Image Analysis

All FDG PET/CT scans were evaluated retrospectively for the presence of abnormal FDG uptake by two board-certified nuclear medicine physicians in consensus (T.F.H., with 6 years of PET experience; K.S., with 3 years of PET experience). All nonintravenous contrast material–enhanced CT scans were evaluated for a residual mass after the end of first-line therapy by two board-certified radiologists in consensus (T.F.H., with 10 years of CT experience; K.S., with 6 years of CT experience).

The mean time between FDG PET/CT and biopsy was 24.6 days (±14.2 days). The maximum standardized uptake value (SUV), defined as the mean value of the three most intense pixels within a lesion, of the histopathologically proved recurrent lesion(s) was compared with that of the false-positive lesion(s).

In 58 patients who underwent posttreatment (<2 months) PET/CT after the end of first-line therapy, the nonenhanced CT scan was evaluated for bulky disease (largest diameter, >5 cm) and persistent disease (T.F.H., K.S.).

Statistical Analysis and Reference Standards

The prognostic effect of bulky disease after the end of first-line therapy was calculated by using the Fisher exact test. Statistical analysis was performed with computer software (StatView, version 5.0.1; SAS Institute, Cary, NC). A confidence level of 95% (a difference with $P < .05$) was considered statistically significant. Negative and positive predictive values, sensitivity, and specificity were calculated by using as the reference standard either the clinical follow-up results in patients with negative findings at FDG PET/CT or the biopsy results of patients with pathologic FDG-avid lesions at PET/CT.

Results

Patients and Disease

In 39 patients with Hodgkin lymphoma (25 male, 14 female; age range, 14–76 years; mean age, 33.0 years ± 12.2) (Table E1, *http://radiology.rsnajnls.org/cgi/content/full/244/1/257/DC1*), no FDG-avid lesions were seen at PET/CT at further follow-up after first-line therapy (Fig 1). The initial disease stages in this group were as follows: Five patients had stage I disease, 22 had stage II disease, five had stage III disease, and seven had stage IV disease. All patients had a disease-free follow-up with a mean observation time of 26.2 months (±12.5 months).

Pathologic FDG-avid lesions were found at PET/CT after first-line therapy in 27 patients (21 male, six female; age range, 11–67 years; mean age, 33.0 years ± 12.2) (Table E2, *http://radiology.rsnajnls.org/cgi/content/full/244/1/257/DC1*). Six patients had persistent disease at posttreatment PET/CT performed within 2 months after the end of treatment, and 21 patients had recurrent disease at follow-up PET/CT. The initial disease stages in the patients with FDG-avid lesions suspicious for recurrent or persistent Hodgkin lymphoma were as follows: Five patients had stage I disease, 14 had stage II disease, five had stage III disease, and three had stage IV disease.

Biopsy

In 23 of the 27 patients (85%) who underwent surgical biopsy (three with stage I disease, 13 with stage II disease, four with stage III disease, and three with stage IV disease), the biopsy results confirmed the presence of

Figure 1

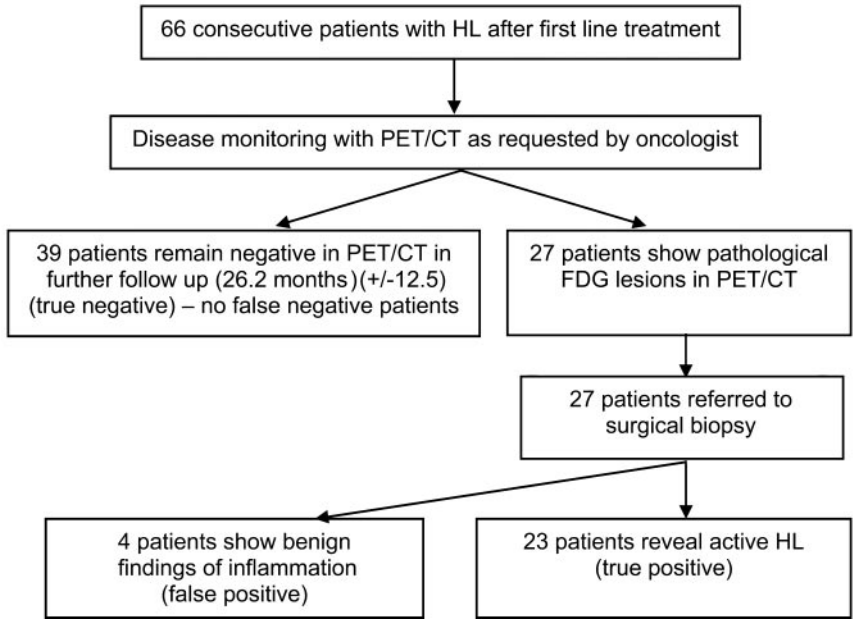

Figure 1: Flow diagram of patients. *HL* = Hodgkin lymphoma.

recurrent or persistent Hodgkin lymphoma.

In the remaining four patients (two patients with stage I disease and one each with stage II and III disease), histopathologic examination revealed inflammatory changes. The locations of the false-positive lesions at FDG PET/CT were as follows: tonsil ($n = 1$) (Fig 2), nasopharyngeal lesion ($n = 1$) (Fig 3), mediastinal lymph nodes ($n = 1$) (Fig 4), and thymus ($n = 1$) (Fig 5). The histopathologic examination revealed bacterial inflammation in the tonsil, a local mast cell proliferation in the nasopharyngeal region, a foam cell accumulation in the mediastinal lymph nodes, and thymic hyperplasia after chemotherapy.

Figure 2

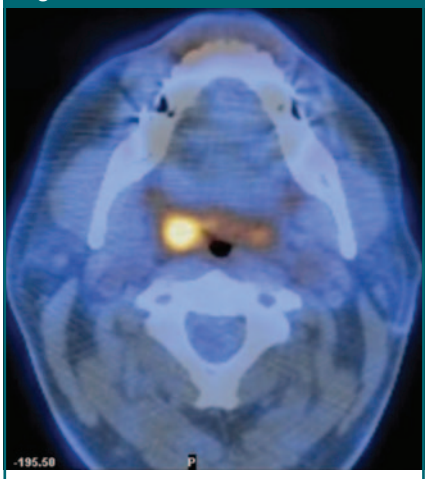

Figure 2: Transverse fused FDG PET/CT scan in 45-year-old patient suspected of having recurrent Hodgkin lymphoma in tonsil area. Note the asymmetric uptake in the right tonsillar region, a finding suspicious for recurrence. Surgical resection revealed inflammation.

Figure 3

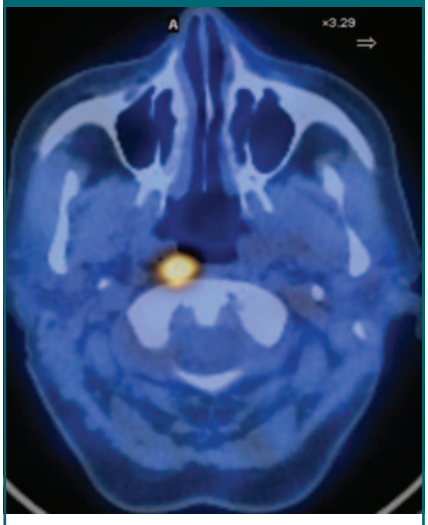

Figure 3: Transverse fused FDG PET/CT scan in 67-year-old patient with persistent FDG avidity in right paramedian nasopharyngeal region after two cycles of chemotherapy and radiation therapy. Surgical biopsy revealed local infiltration with mast cell proliferation.

SUV Values

The mean maximum SUV of the histopathologically proved recurrent lesions was 7.32 (±2.01). The mean maximum SUV of the sites with only inflammatory tissue was 7.30 (±2.53).

Sensitivity and Specificity

When we considered the true-positive results confirmed with biopsy and the true-negative results regarding the mean event-free survival of 26.2 months (±12.5 months), the negative predictive value for FDG PET/CT after first-line therapy was 100% (39 of 39 patients); the positive predictive value, 85% (23 of 27 patients); the specificity, 91% (39 of 43 patients); and the sensitivity, 100% (23 of 23 patients).

Persistent and Bulky Disease

Of the 58 patients who underwent PET/CT within 2 months after the end of first-line therapy and whose PET/CT scans were evaluated for bulky disease, 41 (71%) remained in remission at further follow-up. Two of the 41 patients had bulky disease after the end of therapy. Of the remaining 17 of 58 patients with confirmed recurrence (29%), five had bulky disease after the end of therapy (Table E3, *http://radiology.rsnajnls.org/cgi/content/full/244/1/257/DC1*). The difference between these two groups was significant ($P < .05$, Fisher exact test).

Six of the 58 patients had persistent disease after the end of therapy. Four patients were sent for biopsy after posttreatment PET/CT. In two of the four patients, histopathologic examination revealed active Hodgkin lymphoma; two patients had only benign findings of inflammation and were not referred for further therapy. In the remaining two patients, the treating oncologist decided to perform a further follow-up PET/CT examination after 6 months. Follow-up PET/CT revealed the same sites of FDG uptake. The biopsies of the FDG-avid lesions in these two patients revealed active Hodgkin lymphoma. Thus, of six patients with persistent FDG activity, four had recurrence confirmed with biopsy and received second-line treatment. Two patients had negative findings at biopsy and remained free of recurrence at further follow-up.

Discussion

The results of our study indicate that FDG PET/CT can help confirm the absence of Hodgkin lymphoma after first-line therapy. However, FDG PET/CT can yield false-positive results after first-line therapy, compared with biopsy.

High-dose chemotherapy followed by autologous stem cell transplantation is the accepted therapy for patients with relapse or persistence of Hodgkin lymphoma after first-line therapy (5,6). High-dose chemotherapy followed by autologous stem cell transplantation is a highly toxic chemotherapy regimen. The treatment-related mortality, including death from second malignancy, is 17% at 15 years (7). Treatment-related side effects include hypogonadism, hypothyroidism, unusual infections, depression, and cardiac disease (7). The long-term mortality underscores the importance of a correct assessment of residual or recurrent disease after the end of first-line therapy.

Intravenous contrast-enhanced CT is routinely included in the initial work-up as in the restaging of Hodgkin lymphoma. Findings of Hodgkin lymphoma at CT include lymph node enlargement, osseous alterations, and changes in patterns of contrast enhancement suggestive of organ involvement. Active disease in normal-size lymph nodes, as well as in the spleen and bone marrow, is usually not detected. Magnetic resonance imag-

ing has been shown to be a sensitive tool in the detection of bone marrow involvement at staging (8,9). During the past years, PET with FDG has replaced gallium 67 scintigraphy for clinical staging and demonstrated no difference from conventional morphologic staging methods in depicting nodal and extranodal involvement (10). In addition, assessment of bone marrow disease could be achieved (11). In the assessment of Hodgkin lymphoma after the end of therapy, morphologic imaging modalities are hampered by reduced specificity in excluding disease in residually enlarged lymph nodes (12). Especially for this application, PET has repeatedly demonstrated a high negative predictive value, helping exclude persistent disease (13).

Because of the limited morphologic information obtained at FDG PET to localize the disease, this functional imaging modality has had to be performed as an adjunct to morphologic imaging with intravenous contrast-enhanced CT in the staging of Hodgkin lymphoma. Consequently, the combination of both methods into a single-step FDG PET/CT examination has simplified diagnostic imaging in patients with lymphoma (14). This has been proved in patients with lymphoma and other cancers such as bronchial carcinoma (15–17).

Because of the high negative predictive value of FDG PET/CT, recurrent or persistent disease can reliably be excluded in patients with FDG-negative residual masses. In our study, all pathologic FDG-avid lesions detected with PET/CT were verified with histopathologic examination; four patients had false-positive findings. The cause of the false-positive lesions in these patients could be determined. In three of the four cases of false-positive recurrence, the patient received a combination of radiation therapy and chemotherapy before undergoing PET/CT. The false-positive FDG lesions in these three patients were in the radiation field and could have also been caused by combined radiation therapy and chemotherapy.

It is interesting that the mean maximum SUV of the lesions with histopathologically proved recurrence of Hodgkin disease was equivalent to that of the false-positive lesions with only inflammation tissue. From a qualitative assessment of our data, it appears that the mean maximum SUV is not useful for differentiating between active disease and inflammation.

Bulky disease after first-line therapy has been described as a predictive risk factor for recurrence of Hodgkin lymphoma (1). Our data confirmed that a significantly larger number of patients with bulky disease (>5 cm) than without bulky disease after first-line therapy relapse. The presence of bulky disease after first-line therapy increases the likelihood of recurrent disease and must be taken into account when analyzing PET/CT data. Lower initial stages, absence of abnormal FDG uptake, and no evidence of a bulky mass at first restaging FDG PET/CT are favorable factors regarding successful treatment.

Persistent disease after first-line treatment is a sign of the failure of induction therapy in patients with Hodgkin lymphoma. These patients need further salvage chemotherapy, including high-dose chemotherapy with autologous stem cell support (18). Because of the toxicity of high-dose chemotherapy with autologous stem cell support, persistent Hodgkin lymphoma must be reliably excluded. In our study, six patients had persistent disease. In two patients, active Hodgkin lymphoma could be excluded with biopsy of the FDG-avid lesion. In four patients, biopsy of the FDG-avid lesion revealed active Hodgkin lymphoma; only these patients were referred for further therapy. These findings indicate the importance of histopathologic evaluation before induction of salvage chemotherapy, including high-dose chemotherapy with autologous stem cell support.

Our study had limitations. The study population of 66 patients with Hodgkin disease after first-line therapy was relatively small. The small number of patients reflects the rather low incidence of this disease and the well-defined patient population. Furthermore, the mean follow-up of 26.2 months was rather short because it is well known that

Figure 4

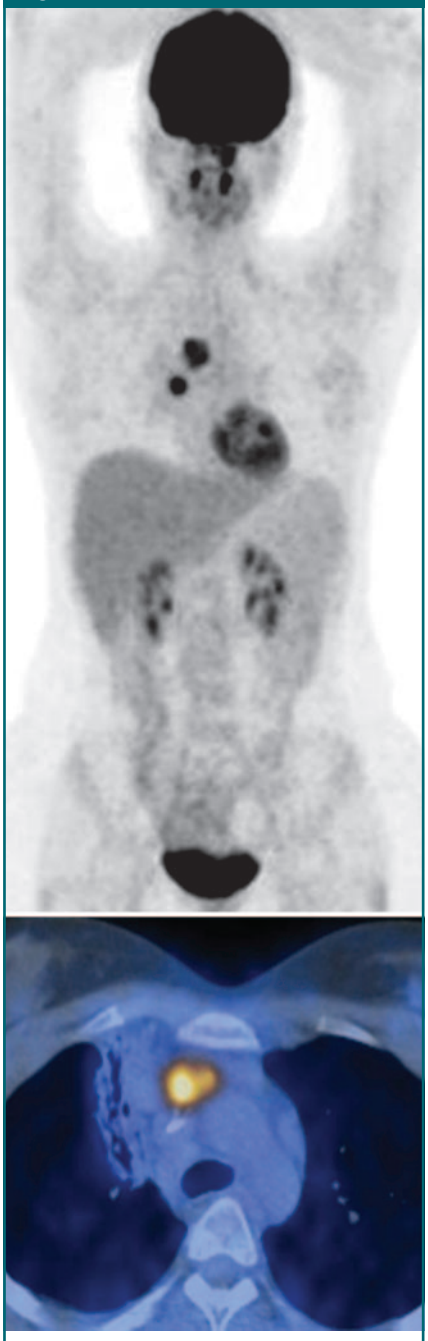

Figure 4: Anterior view of maximum intensity projection FDG PET image (top) and fused transverse FDG PET/CT image (bottom) obtained at the level of the mediastinal region in 23-year-old patient after eight cycles of chemotherapy and radiation treatment. Note the increased FDG uptake in the anterior mediastinum. Histopathologic examination revealed local foam cell accumulation, which consisted of benign macrophages with accumulated lipoproteins.

Hodgkin lymphoma can relapse after longer disease-free intervals, as demonstrated in our study. Last, the considerably high frequency of recurrent disease was due to the tertiary care function of our cancer institute and did not reflect the typical population of patients with Hodgkin lymphoma.

To our knowledge, our study was the first in which all FDG-avid PET/CT lesions were evaluated with histopathologic work-up. Because of ethical reasons, patients with negative findings but persistent bulky disease did not undergo histologic work-up. The disease-free interval was, however, confirmed with follow-up.

We conclude that FDG PET/CT can help exclude the presence of persistent and/or recurrent Hodgkin lymphoma after first-line therapy. Because of the false-positive results and the toxicity of salvage chemotherapy—including high-dose chemotherapy with autologous stem cell support—biopsy of the FDG-avid lesion is still needed, in our opinion.

Figure 5

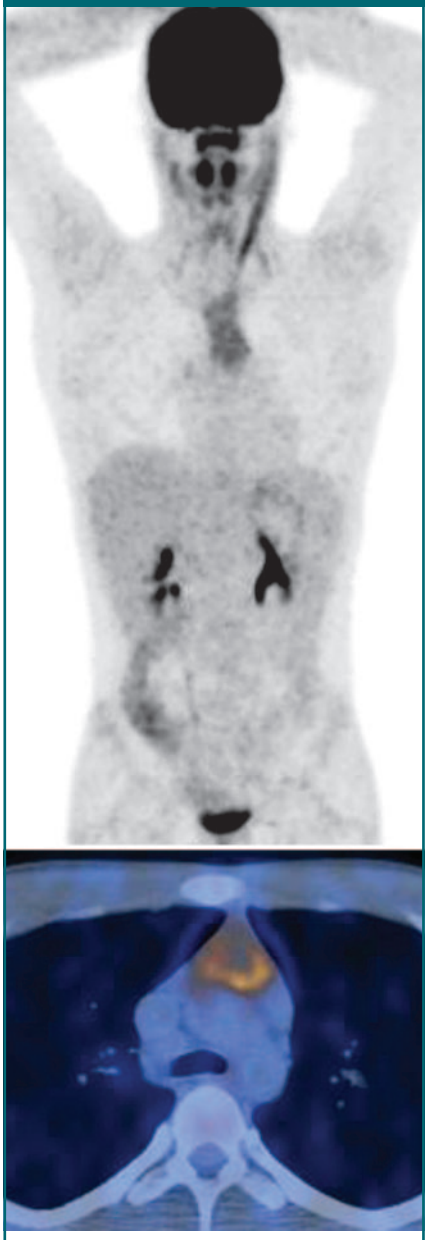

Figure 5: Anterior view of a maximum intensity projection (top) and transverse fused FDG PET/CT image (bottom) in 16-year-old patient with mediastinal FDG avidity after eight cycles of chemotherapy. Histopathologic examination revealed activated thymus tissue but no recurrence of Hodgkin lymphoma after the end of first-line therapy.

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