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R. Crocchiolo, F. Fallanca, G. Giovacchini, A. J. M. Ferreri, A. Assanelli, et al.. Role of FDG-PET/CT in detecting relapse during follow-up of patients with Hodgkin's lymphoma. *Annals of Hematology*, 2009, 88 (12), pp.1229-1236. <10.1007/s00277-009-0752-4>. <hal-00535060>

HAL Id: hal-00535060

<https://hal.science/hal-00535060v1>

Submitted on 11 Nov 2010

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Role of ^{18}F FDG-PET/CT in detecting relapse during follow-up of patients with Hodgkin's lymphoma

R. Crocchiolo · F. Fallanca · G. Giovacchini · A. J. M. Ferreri · A. Assanelli ·
C. Verona · A. Pescarollo · M. Bregni · M. Ponzoni · L. Gianolli · F. Fazio · F. Ciceri

Received: 6 February 2009 / Accepted: 30 April 2009 / Published online: 26 May 2009
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Abstract The role of ^{18}F FDG-PET/CT during follow-up of patients affected by Hodgkin's lymphoma (HL) in complete remission after treatment is not fully elucidated, since a wide use of ^{18}F fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F FDG-PET/CT) in this setting could be limited by a relative high rate of false-positive results. Herein, we summarize a retrospective analysis of 27 patients with Hodgkin's lymphoma in complete remission after the first-line ($n=20$) or salvage ($n=7$) therapy receiving serial ^{18}F FDG-PET/CT scans during follow-up. Out of 165 scans, 13 were suspected for relapse, which was confirmed in seven patients. All relapses were correctly identified by ^{18}F FDG-PET/CT positivity, with a 100% sensitivity; false-positive rate was 46% and negative predictive value was 100%. True-positive findings were mostly associated with multiple sites, subdiaphragmatic involvement, and/or previous sites of disease. According to our results, we conclude that performing routine PET/CT

scan during follow-up of those patients who are at high risk of relapse would be advisable, although caution must be adopted when interpreting PET/CT results due to the relatively high rate of false-positive findings. If FDG abnormal uptake is present at multiple nodal sites, subdiaphragmatic lymph nodes, or previous sites of disease, histological verification of PET abnormal findings is warranted.

Keywords ^{18}F FDG-PET/CT · Hodgkin's lymphoma · Relapse · Follow-up

Introduction

Positron emission tomography/computerized tomography with [^{18}F]fluorodeoxyglucose (^{18}F FDG-PET/CT) represents a powerful imaging tool in the oncological setting since,

R. Crocchiolo · A. Assanelli · A. Pescarollo · F. Ciceri
Hematology and BMT Unit,
San Raffaele Scientific Institute,
Milan, Italy

R. Crocchiolo · A. J. M. Ferreri · A. Assanelli · C. Verona ·
M. Ponzoni · F. Ciceri
Unit of Lymphoid Malignancies,
San Raffaele Scientific Institute,
Milan, Italy

R. Crocchiolo
Biostatistics Unit, University of Genoa,
Milan, Italy

F. Fallanca · G. Giovacchini · L. Gianolli · F. Fazio
Division of Nuclear Medicine,
San Raffaele Scientific Institute,
Milan, Italy

A. J. M. Ferreri
Medical Oncology Unit, San Raffaele Scientific Institute,
Milan, Italy

M. Ponzoni
Pathology Unit, Department of Oncology,
San Raffaele Scientific Institute,
Milan, Italy

M. Bregni
Oncology Unit, Ospedale San Giuseppe,
Milan, Italy

R. Crocchiolo (✉)
Hematology and BMT Unit, Unit of Lymphoid Malignancies,
Department of Oncology, San Raffaele Scientific Institute,
Via Olgettina, 60,
20132 Milan, Italy
e-mail: crocchiolo.roberto@hsr.it

detecting the enhanced glycometabolic activity of neoplastic cells, it is able to define tumor burden and involved organs. In particular, its role in managing lymphoma patients has grown progressively and its use is now often recommended in disease staging [2–5], monitoring during therapy [6–10], posttreatment restaging [11–15], and modeling radiotherapy field [16]. Less is known about the role of ^{18}F FDG-PET during follow-up, especially its capability to detect relapse earlier with respect to CT or ultrasound imaging. So far, only few studies in literature focused on this issue and conclusions are not definite, raising the concern about sensitivity/specificity of the technique in this setting and the need of histological verification of ^{18}F FDG-PET positivity [1, 17, 18]. In aggressive lymphomas, earlier detection is important since a timely salvage treatment is related to better outcome. Thus, it would be important to analyze ^{18}F FDG-PET positivity patterns during follow-up to distinguish patients who should be referred to an immediate surgical biopsy to start further treatment from patients who could be managed with a more conservative observational approach that could be repeating imaging after 2 or 3 months to confirm or avoid biopsy. This clinical issue is useful in both therapeutic choice and correct patient information, but it has not been considered in previous reports on the role of ^{18}F FDG-PET in lymphoma follow-up.

Herein, we report a monocentric retrospective study evaluating the role of ^{18}F FDG-PET/CT in identifying relapse during follow-up of Hodgkin's lymphoma (HL) patients in complete remission after upfront or salvage treatment, with special regard to those factors associated with relapse, in order to identify situations in which histological verification of sites of abnormal FDG uptake should be promptly performed.

Materials and methods

Patients and treatments

Patients affected by HL who obtained complete remission confirmed by PET/CT after upfront or salvage treatment from July 1999 to March 2006 at the Hematology and Bone Marrow Transplantation Unit of our institution entered in the analysis. Visits and PET/CT scans were mostly done every 4 months during the first year, every 6 months in the second and third year, and yearly afterwards. Informed consent was obtained from each patient. Other exams, such as contrast-enhanced CT scans, magnetic resonance imaging (MRI), or bone marrow biopsy, were performed if clinically indicated to confirm or exclude suspicion of relapsing lymphoma localization during follow-up. In case of PET/CT positivity, further imaging with the above-mentioned techniques, confirmatory

biopsy, or prosecution of follow-up at shorter intervals was used to confirm relapse.

Follow-up started with the assessment of PET/CT complete remission until last visit or the day of PET/CT-documented relapse. Last day of observation was the 6th of May 2008.

Treatment modalities were conventional ABVD chemotherapy, four to eight cycles, as first-line treatment; high-dose sequential (HDS) regimen (sequential chemotherapy cycles with: cyclophosphamide 7 g/m^2 followed by peripheral blood stem cell collection; vincristine 1.4 mg/m^2 +methotrexate 8 g/m^2 or alternatively cytarabine 2 g/m^2 twice a day for 4–6 days with stem cell support; etoposide 2 g/m^2 with stem cell support, each cycle performed every 28 days) followed by autologous stem cell transplantation (ASCT) was instead used for relapsed or refractory disease. Conditioning regimen for ASCT was mitoxantrone 60 mg/m^2 plus melphalan 180 mg/m^2 . Patients not in remission before ASCT or who relapsed after ASCT received allogeneic stem cell transplantation. Involved-field radiotherapy was performed in limited-stage patients (stages I and II), on localized extranodal sites or on mediastinal bulky disease, both in limited and advanced disease.

PET/CT studies

PET/CT studies were acquired with two integrated PET/CT systems, either Discovery LS or Discovery ST (GE medical systems, Waukesha, WI, USA). The transaxial full width at half maximum at the center of the field of view is about 5 and 6 mm, for Discovery LS and ST, respectively. All PET scans were performed in two-dimensional mode after injecting about 370 MBq of [^{18}F]FDG (radiochemical purity >95%). Patients refrained from drinking and fasted for at least 6 h before the FDG-PET/CT scan. Blood glucose levels were measured in all subjects before [^{18}F]FDG injection. After a 60-min uptake period, a CT scout was acquired to define the body axial extension (from the pelvis to the base of the skull) to be imaged. Subsequently, a helical CT scan was acquired during shallow breathing. At the end of the CT scan, the bed position was translated into the PET field of view for the PET study and PET data of the whole-body distribution of the tracer were acquired (4 min per bed) in 2-D mode. PET images were reconstructed using an iterative algorithm (ordered subset expectation maximization, 28 subsets, two iterations, matrix 128×128). Attenuation correction was performed using CT images, after the conversion of the CT numbers in linear attenuation coefficients for the 511-keV energy radiation. Correction for dead time, random, and scatter events was also performed. CT and PET images were finally matched and fused into transaxial, coronal, and sagittal images. Image

analysis was performed using a Xeleris WorkStation (General Electric Medical Systems, Waukesha, WI, USA).

PET/CT scans were all revised by two expert nuclear medicine physicians (F.F. and L.G.); visual assessment was used to categorize every PET scan as positive or negative. As reported by Juweid et al. [14], abnormal FDG uptake was defined when focal or diffuse FDG uptake above background was present in a location incompatible with normal anatomy.

Results

Twenty-seven consecutive patients performed a total of 165 ^{18}F FDG-PET/CT scans during the follow-up period (median per patient 5, range 2–15). Median age was 35 years old (range 17–83); median follow-up duration was 34 months (range 4–71). HL was diagnosed at stage I in one patient (4%), II in 12 (44%), III in nine (33%), and IV in five (19%) patients. Twenty patients were in first complete remission after ABVD chemotherapy; six patients were in second complete remission after HDS and ASCT; one patient received allogeneic stem cell transplantation. Nine patients received also consolidation radiotherapy.

Thirteen PET/CT scans were suspected for relapse, showing increased FDG activity compatible with recurrence of disease. Seven of them corresponded to relapse, while six were false-positive findings (Fig. 1). Biopsy was performed in six cases: two were relapses while on four cases reactive follicular hyperplasia ($n=2$), thymic hyperplasia ($n=1$), and fibrotic involution with sclerosis of lymph node parenchyma ($n=1$) emerged from histological examination. Among the seven remaining cases, in two cases, further follow-up showed spontaneous normalization of FDG uptake while for the five true-positive patients CT dimensional abnormalities indicating tumor growth ($n=2$) and clinical assessment ($n=3$) were sufficient to confirm

relapse later on during follow-up, at a median time of 3 months (range 1–6) after PET/CT scan; at the time of first abnormal FDG uptake, in fact, these patients did not present any symptom related to recurrence of disease or radiological abnormality. The same is true for the two relapses confirmed by biopsy (see above): histological confirmation was made through biopsy of deep laterocervical lymph nodes not suspected by clinical examination at the time of abnormal PET/CT.

Regarding the relapse sites, five of the seven relapses presented with FDG abnormal uptake at sites previously involved by disease before treatment and five had multiple lymph node involvement at relapse. Four patients had subdiaphragmatic nodal uptake at the ^{18}F FDG-PET/CT, and, interestingly, three of them had a true relapsing disease. As reported in Table 1, five of the seven patients with positive ^{18}F FDG-PET/CT and relapse had two or three of these features, while only one of the six false-positives (case #9) had more than one of these characteristics (Fisher exact test, $p=0.05$). Conversely, no correlation with B symptoms, extranodal sites, or previous radiotherapy fields emerged (Table 1). True- and false-positive findings (Fig. 2) were distributed equally among patients after first-line and salvage therapy; after first-line: five true- vs. three false-positive cases, after salvage: two true- vs. three false-positive cases. ^{18}F FDG-PET/CT findings are reported in Table 2. True-positive and false-positive PET findings were observed in the same patient, after first-line and salvage treatment, respectively (patient #6).

All relapses in this series occurred within the cases of positive ^{18}F FDG-PET/CT, thus confirming a 100% sensitivity in this setting. Negative and positive predictive values were 100% and 54%; specificity was 70%.

Discussion

The present study confirms the relatively low specificity of ^{18}F FDG-PET/CT in detecting relapse during follow-up of HL patients and suggests more reliable results in the subgroups of HL patients with FDG abnormal uptake at multiple sites, in primary and subdiaphragmatic sites of disease. In a field where evidence-based recommendations are lacking, our data seem to suggest that HL patients with two or three of these features will obtain some benefit from immediate biopsy, while patients with ^{18}F FDG-PET/CT displaying abnormal uptake in only one of these sites could be managed with a more conservative approach.

The increasing interest about ^{18}F FDG-PET/CT use in managing lymphoma patients is demonstrated by the recent consensus on integration of ^{18}F FDG-PET/CT into the standardized response criteria of lymphoma [19]. More recently, some studies indicated that ^{18}F FDG-PET also

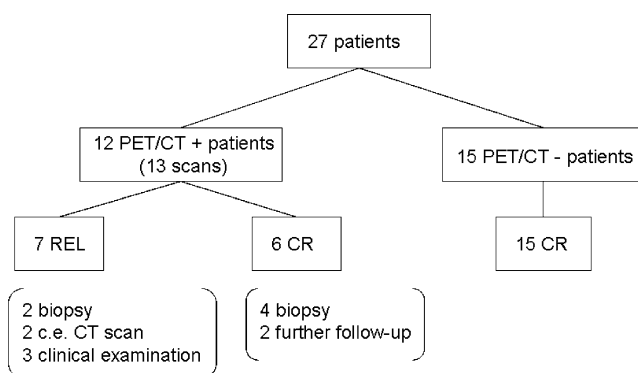


Fig. 1 Algorithm showing PET/CT results. Fifteen patients had no positive PET/CT scans; 12 patients presented with one or more positive PET/CT imaging requiring further appropriate investigations. Final outcomes are shown. REL = relapse; CR = complete remission

Table 1 Patients' characteristics and FDG-PET findings

Diagnosis/relapse			Follow-up								
Pt#	Outcome	No. of sites before Tx	Above (A) or below (B) diaphragm	Extranodal	B symptoms	No. of sites of FDG avidity	Above (A) or below (B) diaphragm	Extranodal	Previous sites of disease	Inside RT field	B symptoms
#3	FP	6	A + B	Y (lung)	N	1	A	Y (lung)	Y	NA	N
#5	TP	2	A	N	N	4	A	N	Y	Y	N
#6 (1)	TP	2	A	N	N	2	A + B	N	N	NA	N
#6 (2)	FP	1	A + B	N	N	2	A	N	N	NA	N
#7	TP	2	A	N	N	2	B	N	N	NA	N
#9	FP	2	A + B	Y (bone)	N	2	A + B	N	N	NA	N
#16	FP	6	A + B	Y (bone, lung)	N	1	A	N	N	NA	N
#19	FP	2	A	N	N	1	A	N	Y	NA	N
#20	TP	2	A	N	N	2	A	N	Y	NA	N
#22	TP	2	A	N	N	1	A	N	Y	N	N
#23	FP	3	A	N	N	1	A	N	Y	Y	N
#24	TP	1	A	N	N	7	A + B	N	Y	Y	Y
#27	TP	2	A	N	Y	1	A	N	Y	NA	N

Patients' characteristics at diagnosis or relapse and characteristics of suspected PET/CT scans are shown here, with regard to site and number of lymph nodal involvement of disease and of FDG avidity

FP false positive, TP true positive, Y yes; N no; NA not applicable

provides useful information about disease status before ASCT and even allogeneic stem cell transplantation in relapsed or refractory HL and non-Hodgkin's lymphoma, with a significant correlation between pretransplant PET status and prognosis [20–26]. CT scan is the most used in restaging lymphoma; however, some authors reported that history and physical examination could be the standard approach to follow-up because in most cases early recurrence is first suspected by the patient himself or by the physician, even with routine screening including CT scans [27, 28]. In general, ^{18}F FDG-PET/CT could be particularly useful in earlier detection of relapse after ASCT could be allowed to face with a limited disease burden that could result in better outcome after allogeneic transplantation [29–31]. In the present series, we found that ^{18}F FDG-PET/CT could be a very useful tool in the identification of recurrence during follow-up for two reasons: first, all relapses occurred with a positive ^{18}F FDG-PET/CT in our series, suggesting that disease recurrence is highly unlikely when a negative ^{18}F FDG-PET/CT scan is present. Second, true-positive findings were associated with multiple sites, subdiaphragmatic involvement, and/or previous sites of disease, indicating that those situations are mostly associated to relapse; therefore, performing histological verification is warranted in these cases and continuing follow-up in the other cases if no other radiological, biochemical, or clinical suspicions of relapse exist. Among the seven true-positive patients, five have been diagnosed as relapsed through further CT scan or clinical examination since they did not receive immediate biopsy; by relying on PET/CT results, a promptly performed biopsy would have anticipated diagnosis of 1–6 months, possibly improving prognosis of these patients. In addition, biopsy could have definitely excluded transformation in other lymphoma subtypes or false-positive studies. Despite some limitations mainly due to the retrospective nature of the present study and the relatively low number of patients analyzed, our conclusions are strengthened by the relevant number of serial ^{18}F FDG-PET/CT scans performed. In addition, the fact that patients were consecutive and treated at the same institution limits possible selection bias or differences due to treatment strategies, which are not always uniform among centers,

Fig. 2 Examples of PET/CT imaging. False- and a true-positive cases are presented here: **a** presence of ^{18}F -FDG uptake in right laterocervical and supraclavicular lymph nodes, interpreted as HL relapse (patient #6, FU6): biopsy was performed and histological examination revealed reactive follicular hyperplasia; **b** PET/CT showing one focal tracer uptake in right anterior mediastinum, at the boundary of the primary lesion (*blue arrow*). A contrast-enhanced CT performed after the PET/CT scan did not reveal abnormalities indicating presence of disease. Subsequent clinical follow-up confirmed relapse (patient #22, FU3)

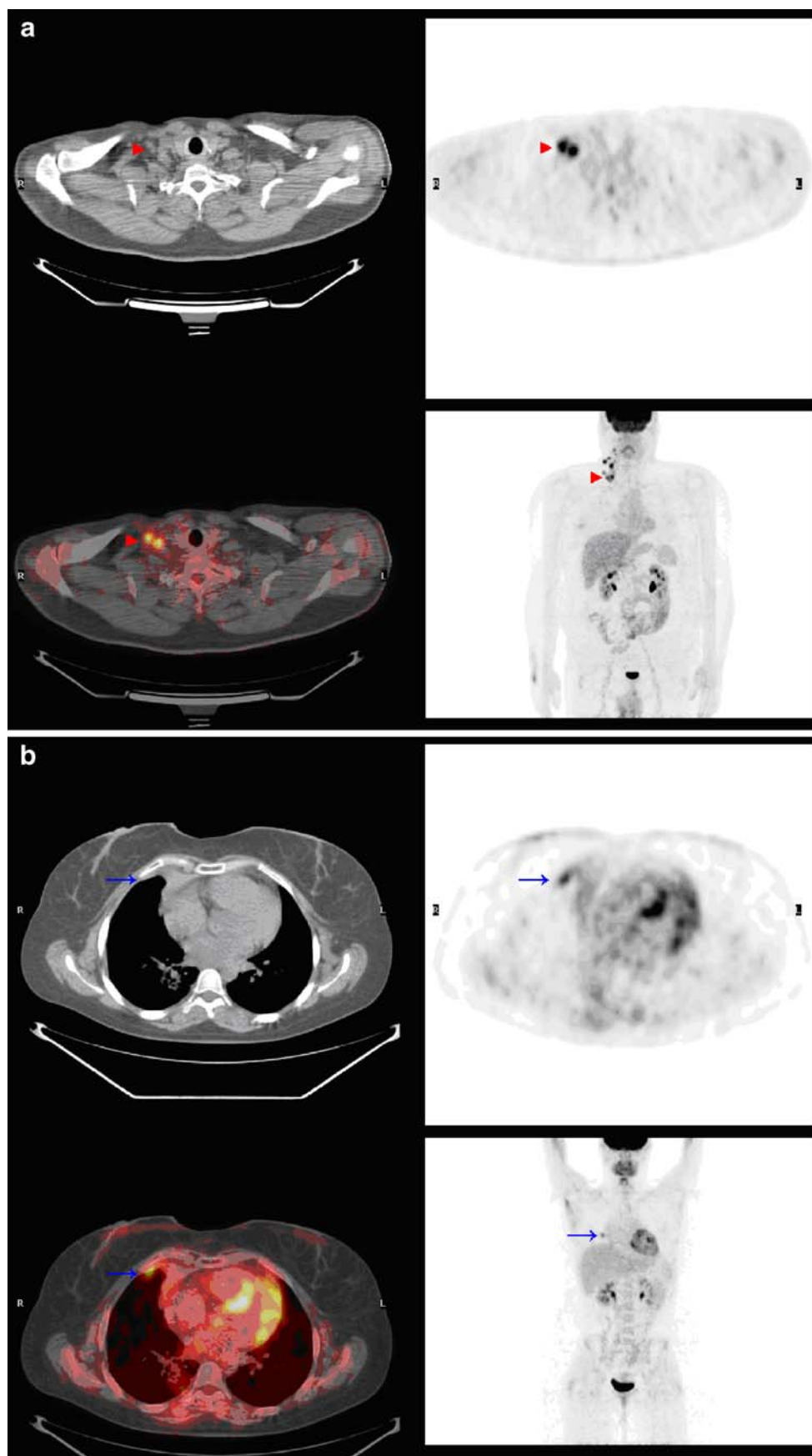


Table 2 PET/CT positive findings during follow-up

Pt.	FU 1	FU 2	FU 3	FU 4	FU 5	FU 6	FU 7	FU 8	FU >8
#3	+	–	–	–	–				
#5	–	–	–	+ ^a					
#6	+	+ ^a	–	–	–	+ ^b	–	–	
#7	–	–	+	+	+ ^c				
#8	–	–	–	–	–	+	–	–	
#9	–	–	–	–	–	+ ^b	–	–	–
#16	–	–	+ ^b	–	–	–	–		
#19	–	+ ^b	–	–					
#20	–	+	+	+	+	+ ^c	+	+	+
#22	–	+	+ ^c						
#24	–	+ ^c							
#27	–	+	+ ^c						

Results of PET/CT scans are presented, with relative outcome: relapse (i.e., true positive) vs. no relapse (i.e., false positive). Only patients with at least one suspected PET/CT scan during follow-up are shown. Bold characters indicate relapsed patients. Patients #9 and #20 performed ten and 13 PET/CT scans, respectively; only the first nine scans are reported here, for graphical reasons. Patient #6 presented a true-positive PET/CT scan after first-line treatment (FU 2); follow-up after second-line therapy started from FU3 and a false-positive PET/CT occurred (FU 6). Patient #20 refused treatment after relapse; follow-up shows persistent PET/CT positivity

FU follow-up visit

^a Relapse confirmed by biopsy

^b Relapse excluded by biopsy

^c Relapse confirmed by clinical follow-up or imaging

especially for relapsed disease. Moreover, all patients performed ¹⁸FDG-PET/CT scans within the same PET/CT system; therefore interpretation of results is derived from technical homogeneity in scan elaboration.

Some previous reports [32, 33] (Table 3) provided the potential role of PET in detecting preclinical relapse but, on the other hand, showed the high false-positive rate, leading to unnecessary biopsies of FDG-avid lesions. Our findings are in line with those reported in literature [17, 18, 32–34], showing a sensitivity and a negative predictive value of 100%, a positive predictive value of 54%, and a false-positive rate of 46%.

Interestingly, Sonet et al. [35] raised the issue of the detection of secondary malignancies by ¹⁸FDG-FDG-PET during posttherapy surveillance of HL patients: in this study, five cases of secondary malignancies were identified (three lung cancers, one epidermoid carcinoma, and one villous tumor) by FDG abnormal avidity. Authors concluded that ¹⁸FDG-FDG-PET might be a new imaging modality for long-term monitoring of late effects, especially second cancer occurrence. Although this is not the aim of the present study, we report that no secondary malignancies were identified among our patients, and this may be due to the relatively low median age short follow-up of our series.

Table 3 Detection of relapse by FDG-PET in follow-up of HL patients: comparison with reported studies

Authors	No. of PET scans	HL pts	Rel/PET+	PPV	FP rate	Spec	Sens	NPV
Jerusalem et al. [17]	119	36	5/11	45%	55%	81%	100%	100%
Levine et al. [32]	156	34	3/28	11%	89%	84%	100%	100%
Meany et al. [33]	57	23	2/11	18%	82%	57%	100%	100%
Schaefer et al. [18]	NR	66	23/27	85%	15%	91%	100%	100%
Zinzani et al. [34]	605	160	51/64	79%	21%	98%	100%	100%
Current study	165	27	7/13	54%	46%	70%	100%	100%

Here are presented results from previously published studies on PET/CT reliability of identifying relapse, both in adult and pediatric setting. Outcomes are reported as fraction of relapses on all PET/CT positive findings, positive predictive value, false-positive rate, specificity, sensitivity, and negative predictive value

Rel relapsed patients, PPV positive predictive value, FP false positive, Spec specificity, Sens sensitivity, NPV negative predictive value, NR not reported

In conclusion, our results indicate that ^{18}F FDG-PET/CT represents a sensitive test during postremission follow-up of HL patients after completion of therapy. Balancing overall costs and potential benefits, we would recommend the performance of a routine PET/CT scan during follow-up of those patients who are at high risk of relapse, especially in the first and second year after the end of treatment; however, due to the high rate of false-positive findings, caution must be adopted when interpreting PET/CT results. When at least two among multiple, subdiaphragmatic, and previously involved sites show abnormal FDG uptake, a confirmatory biopsy is suggested to start timely salvage therapy; in the other cases, further follow-up is advisable, always taking into account patient's medical history, symptoms, and other imaging information.

Acknowledgments We are grateful to all doctors and nurses involved in the care of patients of the Hematology and BMT Unit and Nuclear Medicine Division.

References

1. Zinzani PL, Tani M, Trisolini R et al (2007) Histological verification of positive positron emission tomography findings in the follow-up of patients with mediastinal lymphoma. *Haematologica* 92:771–777. doi:10.3324/haematol.10798
2. Isasi CR, Lu P, Blaufox MD (2005) A meta-analysis of ^{18}F -2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. *Cancer* 104:1066–1074. doi:10.1002/cncr.21253
3. Rigacci L, Vitolo U, Nassi L et al (2007) Positron emission tomography in the staging of patients with Hodgkin's lymphoma. A prospective multicentric study by the Intergruppo Italiano Linfomi. *Ann Hematol* 86:897–903. doi:10.1007/s00277-007-0356-9
4. Schaefer NG, Strobel K, Taverna C et al (2007) Bone involvement in patients with lymphoma: the role of FDG-PET/CT. *Eur J Nucl Med* 34:60–67. doi:10.1007/s00259-006-0238-8
5. Hernandez-Maraver D, Hernandez-Navarro F, Gomez-Leon N et al (2006) Positron emission tomography/computed tomography: diagnostic accuracy in lymphoma. *Br J Haematol* 135:293–302. doi:10.1111/j.1365-2141.2006.06284.x
6. Gallamini A, Hutchings M, Rigacci L et al (2007) Early interim 2- ^{18}F fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian–Danish study. *J Clin Oncol* 25:3746–3752. doi:10.1200/JCO.2007.11.6525
7. Hutchings M, Loft A, Hansen M et al (2006) FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood* 107:52–59. doi:10.1182/blood-2005-06-2252
8. Haioun C, Itti E, Rahmouni E et al (2005) ^{18}F fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. *Blood* 106:1376–1381. doi:10.1182/blood-2005-01-0272
9. Querellou S, Valette F, Bodet-Milin C et al (2006) FDG-PET/CT predicts outcome in patients with aggressive non-Hodgkin's lymphoma and Hodgkin's disease. *Ann Hematol* 85:759–767. doi:10.1007/s00277-006-0151-z
10. Schot BW, Zijlstra JM, Sluiter WJ et al (2007) Early FDG-PET assessment in combination with clinical risk scores determines prognosis in relapsed lymphoma. *Blood* 109:486–491. doi:10.1182/blood-2005-11-006957
11. Spaepen K, Stroobants S, Dupont P et al (2001) Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (^{18}F FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is ^{18}F FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol* 19:414–419
12. Spaepen K, Stroobants S, Dupont P et al (2001) Can positron emission tomography with ^{18}F -fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity? *Br J Haematol* 115:272–278. doi:10.1046/j.1365-2141.2001.03169.x
13. Weihrauch MR, Re D, Scheidhauer K et al (2001) Thoracic positron emission tomography using ^{18}F -fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. *Blood* 98:2930–2934. doi:10.1182/blood.V98.10.2930
14. Juweid ME, Stroobants S, Hoekstra O et al (2007) Use of positron emission tomography for response assessment of lymphoma: consensus of the imaging subcommittee of International Harmonization Project in lymphoma. *J Clin Oncol* 25:571–578. doi:10.1200/JCO.2006.08.2305
15. Kobe C, Dietlein M, Franklin J et al (2008) Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. *Blood* 112:3989–3994. doi:10.1182/blood-2008-06-155820
16. Hutchings M, Loft A, Hansen M et al (2007) Clinical impact of FDG-PET/CT in the planning of radiotherapy for early-stage Hodgkin lymphoma. *Eur J Haematol* 78:206–212. doi:10.1111/j.1600-0609.2006.00802.x
17. Jerusalem G, Beguin Y, Fassotte MF et al (2003) Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. *Ann Oncol* 14:123–130. doi:10.1093/annonc/mdg011
18. Schaefer HG, Taverna C, Strobel K et al (2007) Hodgkin disease: diagnostic value of FDG PET/CT after first-line therapy - is biopsy of FDG-avid lesions still needed? *Radiology* 244:257–262. doi:10.1148/radiol.2441060810
19. Cheson BD, Pfistner B, Juweid ME et al (2007) Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579–586. doi:10.1200/JCO.2006.09.2403
20. Crocchiolo R, Canevari C, Assanelli A et al (2008) Pre-transplant FDG-PET predicts outcome in lymphoma patients treated with high-dose sequential chemotherapy followed by autologous stem cell transplantation. *Leuk Lymphoma* 49:727–733. doi:10.1080/10428190701885545
21. Cremerius U, Fabry U, Wildberger JE et al (2002) Pre-transplant positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (FDG) predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 30:103–111. doi:10.1038/sj.bmt.1703607
22. Schot BW, Pruim J, van Imhoff GW et al (2006) The role of serial pre-transplantation positron emission tomography in predicting progressive disease in relapsed lymphoma. *Haematologica* 91:490–495
23. Filmont JE, Czernin J, Yap C et al (2003) Value of ^{18}F -fluorodeoxyglucose positron emission tomography for predicting the clinical outcome of patients with aggressive lymphoma prior to and after autologous stem-cell transplantation. *Chest* 124:608–613. doi:10.1378/chest.124.2.608

24. Svoboda J, Andreadis C, Elstrom R et al (2006) Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation. *Bone Marrow Transplant* 38:211–216. doi:[10.1038/sj.bmt.1705416](https://doi.org/10.1038/sj.bmt.1705416)
25. Derenzini E, Musuraca G, Fanti S et al (2008) Pre-transplantation positron emission tomography scan is the main predictor of autologous stem cell transplantation outcome in aggressive B-cell non-Hodgkin lymphoma. *Cancer* 113:2496–2503. doi:[10.1002/cncr.23861](https://doi.org/10.1002/cncr.23861)
26. Doderio A, Crocchiolo R, Patriarca F et al (2007) Prognostic value of positron emission tomography (PET) scan in patients with relapsed Hodgkin lymphoma or aggressive non-Hodgkin lymphoma receiving salvage chemotherapy followed by reduced-intensity allogeneic stem cell transplantation. *Blood* Abs#3039
27. Torrey MJ, Poen JC, Hoppe RT (1997) Detection of relapse in early-stage Hodgkin's disease: role of routine follow-up studies. *J Clin Oncol* 15:1123–1130
28. Radford JA, Eardley A, Woodman C et al (1997) Follow up policy after treatment for Hodgkin's disease: too many clinic visits and routine tests? A review of hospital records. *BMJ* 314:343–346
29. Baron F, Storb R, Storer BE et al (2006) Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation. *J Clin Oncol* 24:4150–4157. doi:[10.1200/JCO.2006.06.9914](https://doi.org/10.1200/JCO.2006.06.9914)
30. Corradini P, Doderio A, Farina L et al (2007) Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. *Leukemia* 22:2316–2323. doi:[10.1038/sj.leu.2404822](https://doi.org/10.1038/sj.leu.2404822)
31. Freytes CO, Loberiza FR, Rizzo JD et al (2004) Myeloablative allogeneic hematopoietic stem cell transplantation in patients who experience relapse after autologous stem cell transplantation for lymphoma: a report of the International Bone Marrow Transplant Registry. *Blood* 104:3797–3803. doi:[10.1182/blood-2004-01-0231](https://doi.org/10.1182/blood-2004-01-0231)
32. Levine JM, Weiner M, Kelly KM (2006) Routine use of PET scans after completion of therapy in pediatric Hodgkin disease results in a high false positive rate. *J Pediatr Hematol Oncol* 28:711–714. doi:[10.1097/01.mph.0000243648.66734.eb](https://doi.org/10.1097/01.mph.0000243648.66734.eb)
33. Meany HJ, Gidvani VK, Minniti CP (2007) Utility of PET scans to predict disease relapse in pediatric patients with Hodgkin lymphoma. *Pediatr Blood Cancer* 48:399–402. doi:[10.1002/pbc.20797](https://doi.org/10.1002/pbc.20797)
34. Zinzani PL, Stefoni V, Tani M et al (2009) Role of [18F] fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *J Clin Oncol* 27:1781–1787
35. Sonet A, Graux C, Nollevaux NC et al (2007) Unsuspected FDG-PET findings in the follow-up of patients with lymphoma. *Ann Hematol* 86:9–15. doi:[10.1007/s00277-006-0167-4](https://doi.org/10.1007/s00277-006-0167-4)