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Lugano classification: response evaluation criteria for positron emission tomography/computed tomography in lymphoma follow-up

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Abstract

Background: The purpose of this study is to assess the role of 18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET-CT) in the follow-up of patients with lymphoma after finishing therapy.

Results: This study included 42 lymphomas (25 non-Hodgkin's lymphoma and 17 Hodgkin's lymphoma); patients ranging in age from 18 to 70 years were examined by ^{18}FDG PET-CT after therapy and analyzed retrospectively. Confirmatory biopsy was mandatory in cases of suspected disease recurrence and follow-up in cases of complete metabolic response. Positron emission tomography/computed tomography in assessment of lymphoma treatment response reveals significant statistical significance ($P < 0.05$). It shows 100% sensitivity, 92.8% specificity, and 95.2% accuracy in the prediction of response.

Conclusion: Positron emission tomography/computed tomography plays an important role in detection of response to treatment of lymphoma after finishing therapy.

Keywords: Lymphoma, PET, CT, Lugano classification

Background

Fluorodeoxyglucose positron emission tomography/computerized tomography (^{18}FDG PET/CT) [1] is a powerful imaging modality in the field of oncology since it detects the enhanced glycometabolic activity of neoplastic cells, with the ability to define tumor burden and involved organs. Its role in managing lymphoma patients has grown progressively, and its use is now often recommended in [2–5], monitoring the therapy [6–15], and its modeling [16].

So far, only few studies in literature focused on the role of ^{18}FDG PET during follow-up, especially its capability to detect relapse earlier with respect to CT or ultrasound imaging issue. The conclusions are not definite, raising the concern about sensitivity and specificity of the technique in this setting and the need of histological verification of ^{18}FDG PET positivity [1]. In aggressive lymphomas, earlier detection is important since a timely salvage treatment is related to better outcome. Thus, analyzing ^{18}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 [2, 4].

The clinical response based on PET-CT scans was defined in 2007 by the International Harmonization

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Project criteria [3, 4], and interpretation of PET was subsequently standardized by the proposal of the Deauville criteria for grading the degree of FDG avidity in comparison to the mediastinal blood pool and liver [5]. The Lugano classification, published in 2014, aimed to simplify and standardize baseline and response assessment and confirm the role for FDG PET-CT in lymphoma. Current study will assess the role of functional imaging with FDG PET-CT in lymphoma at the end of treatment and follow-up [17].

The most recent system proposed for response assessment, known as the Lugano classification [17], applies to both Hodgkin and non-Hodgkin lymphoma. The use of standardized criteria for response assessment is important for making accurate treatment decisions and for determining the direction of further research. This review provides an overview of the updated PET-CT response criteria to familiarize the radiologist with the most important and clinically relevant aspects of lymphoma imaging [15, 16].

The Lugano classification proposes new definitions relevant to imaging in lymphoma: for splenomegaly, vertical length of spleen greater than 13 cm; for measurable adenopathy, nodal long-axis diameter greater than 1.5 cm (a unidimensional measurement) [5–10].

Response at FDG PET/CT is graded on the five-point scale and categorized as complete metabolic response (scores 1, 2, 3), partial metabolic response (score 4 or 5 with reduced FDG uptake), no metabolic response (score 4 or 5 with no significant change in FDG uptake), or progressive metabolic disease (score 4 or 5 with increased FDG uptake or new lesions compared to previous scan) [3, 4].

Methods

Current study is a retrospective study comprised of 42 patients, referred from the oncology department, ranging in age from 18 to 70 years. The study was conducted during the period from July 2016 till January 2018 and approved by the local research ethical committee at our university.

Inclusion criteria included patient affected with lymphoma and underwent surgical resection or chemotherapy or radiotherapy, in which imaging was done before and after 6 months from treatment, with no age or sex predilection in patient selection. On the other hand, pregnant females, patients with history of previous hypersensitivity reaction to contrast material, and patients with renal failure were excluded from the study. A detailed history taking and informed consent were obtained from all patients.

Patient's preparation

Participants avoided strenuous exercise for 24 h and fasted for at least 4 h before examination. Blood glucose level should be below 200 mg/dl in which diabetic patients relevant considerations before the study include restrictions of diet and activity and management of blood glucose levels in diabetic patients, as well as an awareness of the effect of medications and environmental conditions. The patient was asked to void before scan.

PET-CT technique

A dedicated PET scanner (DST PET/CT; Discovery ST PET-CT, General Electric Medical Systems, Milwaukee, WI, USA) was used, and the radiopharmaceutical used was 18F-FDG. All examinations were carried out using two integrated PET-CT scanners (Ingenuity TF 128; Philips Healthcare, Cleveland, OH, USA) 1 h after intravenous administration of 7–11 mCi of 18F-FDG corresponding to the patient's body weight. Blood glucose level should be less than 200 at time of 18F-FDG injection, if more, no injection is done. The time of 18F-FDG injection to the scan is 45 min.

Multidetector computed tomography diagnostic post contrast examination was taken after I.V. non-ionic contrast administration for attenuation correction. The contrast agent iopromide (Ultravist) (300 mg of iodine/ml) was used at a dose of 100–120 ml corresponding to the patient's body weight with a 3-ml/s infusion rate, following the administration of 50 ml of a normal saline chaser at a 3-ml/s infusion rate. Anatomic localization followed by PET images from the skull vault to the mid-thigh was obtained. Images of CT and corresponding functional PET

Table 1 Modified Deauville score

Score	Definition
1	No uptake above background
2	Uptake at an initial site that is less than or equal to mediastinum
3	Uptake at an initial site that is greater than mediastinum but less than or equal to liver
4	Uptake at an initial site that is moderately increased compared to the liver at any site
5a	Uptake at an initial site that is markedly increased compared to the liver
5b	Uptake markedly increased compared to the liver at any new site that is possibly related to lymphoma
X	New areas of uptake unlikely related to lymphoma

Table 2 Demographic data of the studied patients (No. = 42)

Demographic data	All studied patients (***n*** = 42)	
	No.	%
Gender		
Female	25	60%
Male	17	40%
Age		
Mean ± SD	40 ± 15	
Median (range)	37 (18–70)	

images were taken in axial, coronal, and sagittal planes. Patient's height and weight were measured. SUV average of reference hepatic activity was measured according to the hepatic activity, and SUV was calculated according to the lean body mass.

Image analysis

Analysis of PET-CT images was performed with correlation to Deauville criteria (Table 1) [17]. We measured maximum dimensions of the enlarged lymph nodes or extranodal tissues. A lesion was considered positive if there is abnormal FDG uptake greater than surrounding tissue and not related to physiologic uptake sites (e.g., myocardium). Maximum standardized uptake values (SUV max) were then measured.

Statistical analysis

All data were collected, tabulated, and analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean ± SD and median (range), and qualitative data were expressed as absolute frequencies (number and percentage). Percent of categorical variables was

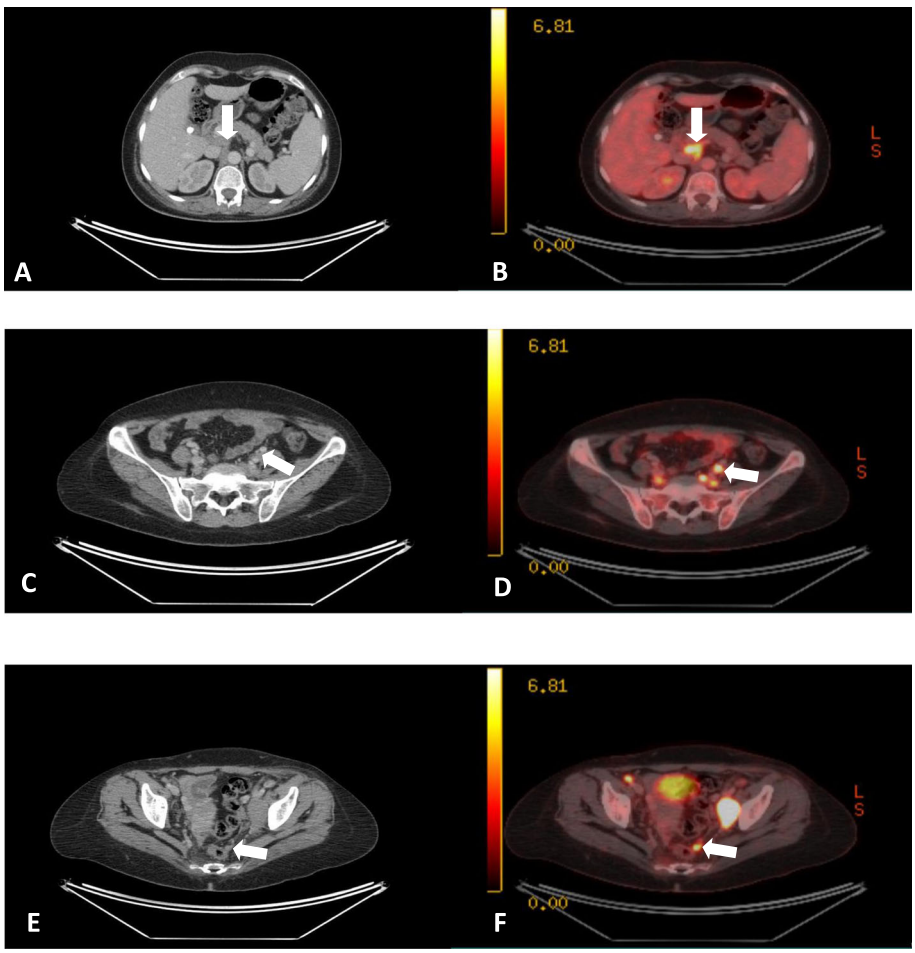

Fig. 1 Thirty-seven-year-old patient, known case of non-Hodgkin lymphoma. Multiple infradiaphragmatic metabolically active lymph nodes seen at the following sites: celiac, aortocaval, precaval (**a** and **b**); paraaortic, bilateral common iliac, bilateral internal (**c** and **d**); and external iliac and left para rectal (**e** and **f**), with the largest in precaval measuring 23.3 × 14.7 mm with SUV max 10.5, consistent with a score of 4 on the five-point scale

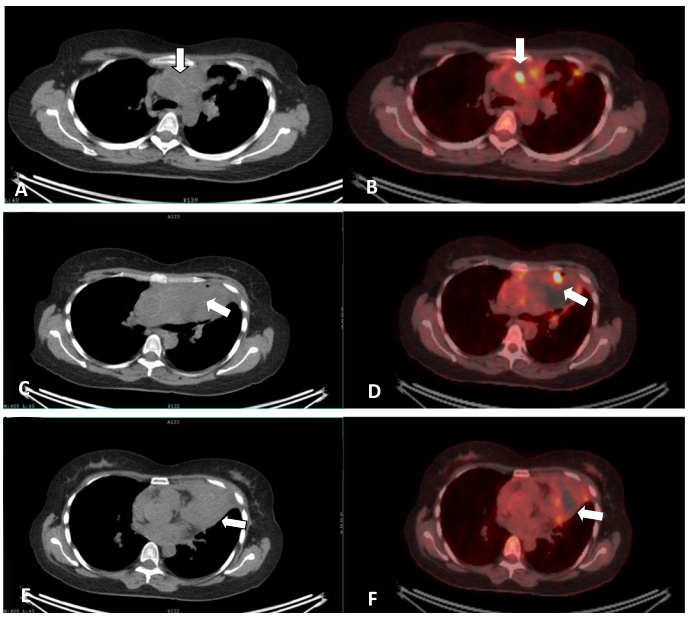

Fig. 2 Thirty-five-year-old female patient, known case of lymphoma. **a**–**f** Anterior mediastinal mass lesion comprising matted lymph nodes. This necrotic infiltrative lesion measures 8 × 6 × 5 cm, showing preferential avid FDG uptake of SUV max 21.4, consistent with a score of 4 on the five-point scale

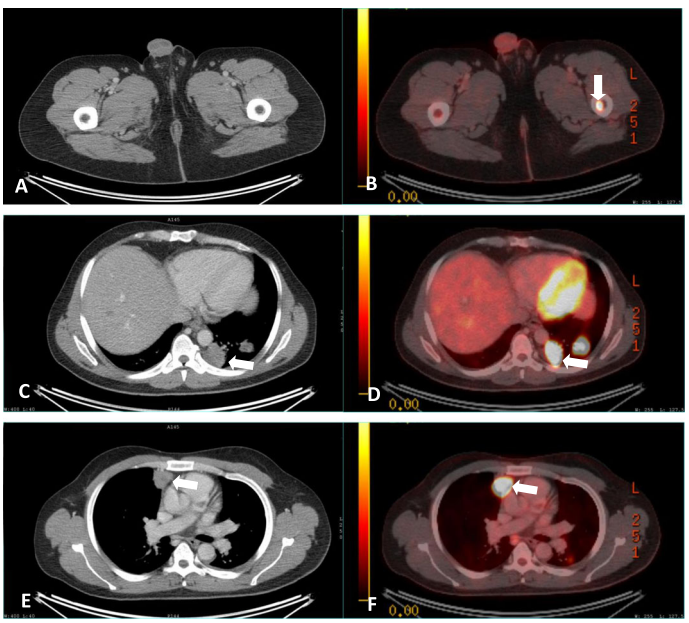

Fig. 3 Thirty-one-year-old male patient with history of NHL received CTH. Multiple variable-sized marrow infiltrative lesions largest seen at left femur (**a** and **b**) with Max SUV of 25. Bilateral multiple variable-sized metabolically active nodules are seen involving lung parenchyma (**c**–**f**) in which the largest on the right side seen involving the right medial segment of middle lobe measuring 30 × 27 mm and SUV max = 302, and on the left side, the largest nodule is seen at postero-medial segment of lower lobe measuring 25 × 29 mm. SUV max = 24, consistent with a score of 5 on the five-point scale

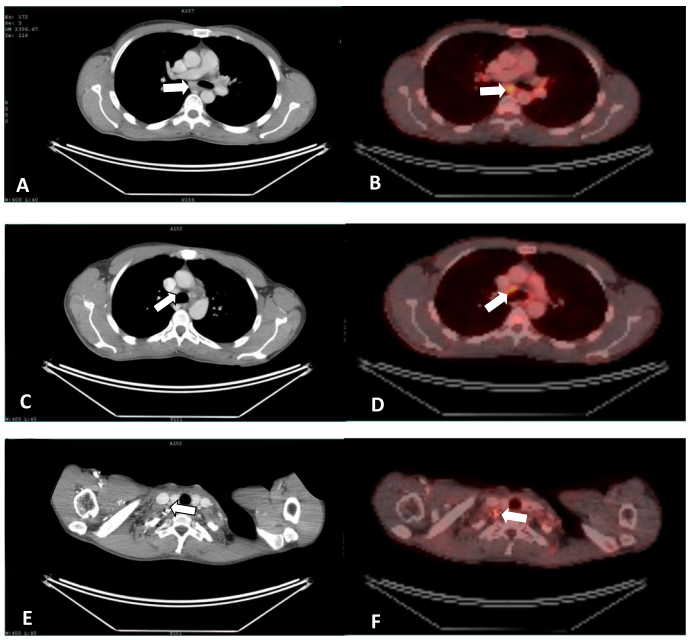

Fig. 4 Forty-two-year-old male patient, known case of Hodgkin lymphoma. Metabolically active pretracheal (**a**–**d**) and aortopulmonary LN groups, largest measures 1.4 × 0.8 cm with SUV max = 7.2 and multiple low metabolically active small retrocaval, paraaortic, and left common iliac (**e** and **f**) (likely inert lymph nodes) with SUV max 2.2, consistent with a score of 3 on the five-point scale

compared using ANOVA. All tests were two sided. *P* value < 0.05 was considered statistically significant (S), and *P* value ≥ 0.05 was considered statistically insignificant (NS).

Results

This study included 42 patients (Table 2); their ages ranged from 18 to 70 years (mean ± SD for age was 40 ± 15). Seventeen cases had Hodgkin lymphoma (40%); 25 cases had non-Hodgkin lymphoma (60%). All cases were pathologically proven prior to imaging either by surgical or imaging-guided biopsy.

Regarding nodal affection, 26 cases had supradiaphragmatic LNs, 9 cases had infradiaphragmatic LNs, and 7 cases had both supradiaphragmatic and infradiaphragmatic LNs. Lymph nodes were either solitary lymph nodes (range from 1 to 3 cm) or amalgamated lymph nodes (range from 5 to 25 cm).

Extranodal involvement (Fig. 1) was detected in 13 cases, 10 cases with bony lesions, 2 cases with pulmonary nodules (Fig. 2), 2 cases with splenic involvement, 1 case with renal involvement, 1 case with thymic involvement, 1 case with thyroid involvement, and 1 case with subcutaneous involvement.

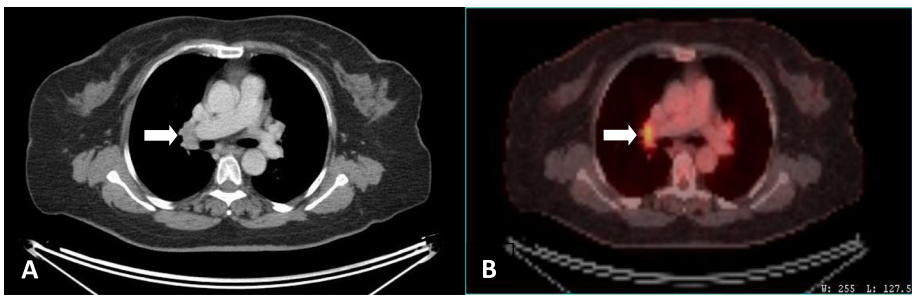

Fig. 5 Fifty-two-year-old patient presented with history of right ovarian malignant lymphoma underwent surgical resection and received CTH, for follow-up. CECT reveals enlarged bilateral hilar LNs (**a**). PET-CT (**b**) shows bilateral hilar FDG avid LNs; the largest is on the right side measuring 19 × 13 mm with SUV max 6.46, consistent with a score of 5b on the five-point scale

Table 3 Treatment response of patients according to Lugano classification

Type of response	Number of patients
Stationary	1
Progressive metabolic response	13
Partial metabolic response	5
Complete metabolic response	23

The follow-up of our cases revealed 9 cases with newly developed lesions: 7 cases developed newly nodal lesions, 1 case developed hepatic focal lesions, and 1 case developed bony lesions (Fig. 3).

In the current study, regarding the SUV max of lymph nodes before therapy ranged from 3 to 15 with mean = 7.21, SUV max after therapy ranged from 2.4 to 25 with mean = 7.08.

The treatment of our cases was as follows: 1 case received bone marrow transplant (BMT) and chemotherapy (CTH), 35 cases received chemotherapy, 3 cases received chemotherapy and radiotherapy (RTH), and 3 cases received surgical resection and chemotherapy (Figs. 4 and 5).

According to Lugano classification, PET-CT (Table 3) showed 1 patient with stationary disease, 13 patients with progressive metabolic response, 5 patients with partial metabolic response, and 23 patients with complete metabolic response (Figs. 6 and 7).

Grading of lymphoma FDG avidity on PET-CT according to Deauville criteria was as shown in Table 4.

In the current study, 18 cases out of 42 patients which proved to have disease progression either (partial or progressive metabolic response) by the PET/CT, the biopsy results of 16 out of the 18 cases proved to be positive, while 2 cases proved to be negative by biopsy.

Comparison of PET-CT and biopsy results in assessment of treatment response reveals significant statistical difference ($P < 0.05$). Hence, PET-CT achieved sensitivity = 100%, specificity = 92.8%, accuracy = 95%, positive predictive value = 88.9%, and negative predictive value = 100%.

Discussion

Lymphoma is considered the most common primary malignancy of hematopoietic origin [18]. Positron emission tomography (PET) using 18 F-FDG integrated with computed tomography (CT) (PET/CT) has become widely used in the diagnosing, staging, and evaluation of therapy response in lymphomas [19].

The Lugano classification [20] stated that bone marrow biopsy may be obviated in patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma if FDG PET-CT is clearly positive for marrow involvement. Bone marrow biopsy may remain necessary in other patients depending on the clinical question and lymphoma histology. In the spleen, focal lesions with FDG avidity above background in typically avid lymphomas are strongly suggestive of splenic lymphoma, as is diffuse FDG avidity of the pretreatment spleen greater than that of the liver. The uptake FDG by gastrointestinal tract lymphoma is variable but may be detected on FDG PET-CT images in 60 (for mucosa associated lymphoma [21]) to 100% (for large cell lymphoma) of cases.

In current study, we investigated the role of PET-CT scan in the follow-up of treatment response in 42 patients in which 17 cases (40.4%) were HL and 25 cases (59.6%) were NHL. The most important result in this study was 23 cases showed CMR and only case had stationary MR. Also, out of 42 cases, 13 showed progressive MR and 5 cases showed partial MR. A biopsy was taken from the 18 cases in which 16 out of 18 were positive and the other 2 were negative. So, in 42 patients with lymphoma, PET attained 100% sensitivity, 92.8% specificity, and 95.2% accuracy in the prediction of response.

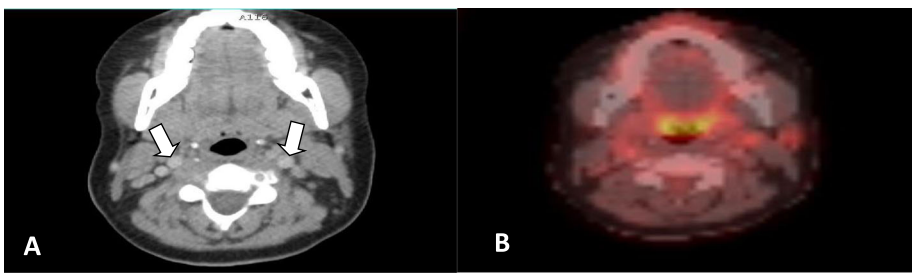

Fig. 6 Twenty-year-old patient, known case of treated Hodgkin lymphoma, finished chemotherapy. Few bilateral deep cervical LNs (**a** and **b**) of low grade metabolic activity are noted reaching up to 2.5 SUV max, mostly reactive in nature, consistent with a score of 1 on the five-point scale

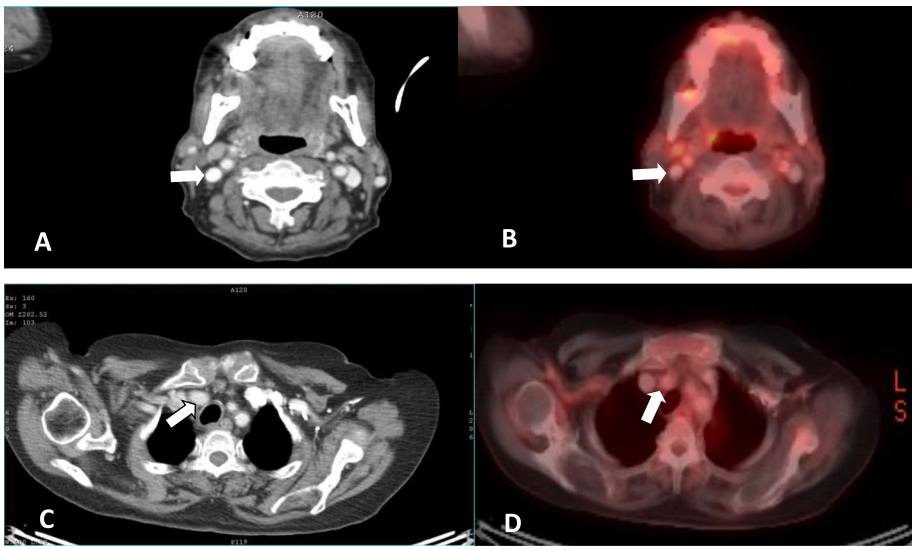

Fig. 7 Twenty-three-year-old patient, known case of Hodgkin lymphoma. Bilateral subcentimetric non FDG avid cervical LNs (**a** and **b**). Non FDG avid mediastinal LNs and thymic hyperplasia (**c** and **d**) with low grade metabolic activity with SUV max 4.14, consistent with a score 2 on the five point scale

Zijlstra et al. [22] included 15 studies, involving 705 patients; all patients were for post treatment evaluation and residual masses; their sensitivity and specificity for detection of residual disease in non-Hodgkin's lymphoma were 72% and 100%, respectively; these results agree with current study as PET showed high sensitivity (100%) and specificity (92%) in prediction of disease recurrence; also, current study results agree with Lavely et al. [23] who studied 20 patients with non-Hodgkin's lymphoma after completion of therapy and they found that FDG-PET prediction of relapse had sensitivity of 100% and a specificity of 84%. Schaefer et al. [4] in a study of 66 patients with HL reported ranges for the sensitivity and specificity of PET-CT in predicting disease relapse with biopsy confirmation which were 100% and 91%, respectively.

Table 4 Modified Deauville criteria of all studied patients

Modified Deauville criteria	All studied patients (***n*** = 42)	
	No.	%
1	12	28.5%
2	10	23.8%
3	3	7.1%
4	4	9.5%
5a	5	11.9%
5b	8	19%

Some previous reports [24, 25] (Table 5) 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 [4, 16, 24–26], showing a sensitivity and a negative predictive value of 100%, a positive predictive value of 54%, and a false positive rate of 46%. Limitations of our study include high cost and small number of patients. More studies are recommended with larger number of patients.

Conclusion

The lymphomas are a heterogeneous group of malignancies. PET-CT plays an important role in detection of response to treatment of lymphoma after finishing therapy.

Table 5 Prognostic values of PET scan of HL patients

Authors	No. of PET scans	HL pts	Rel/PET+	FP rate	Spec	Sens
Jerusalem et al. [16]	119	36	5/11	55%	81%	100%
Levine et al. [24]	156	34	3/28	89%	84%	100%
Meany et al. [25]	57	23	2/11	82%	57%	100%
Schaefer et al. [4]	NR	66	23/27	15%	91%	100%
Zinzani et al. [1, 26]	605	160	51/164	21%	98%	100%
Current study	42	17	5/17	70%	92.3%	100%

Abbreviations
BMT: Bone marrow transplantation; CMR: Complete metabolic response; CTH: Chemotherapy; FDG: Fluorodeoxyglucose; HL: Hodgkin's lymphoma; MDCT: Multidetector computed tomography; NHL: Non-Hodgkin's lymphoma; PET-CT: Positron emission tomography–computed tomography; PMR: Partial metabolic response; RTH: Radiotherapy; SUV max: Maximum standardized uptake value

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Authors' contributions
AL and SS conceived and designed the analysis. SR collected the data, performed the analysis, and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the ethical committee of Ain Shams University on June 2016 (no reference number was given at that time). All patients included in this study gave written informed consent to participate in this research by the patients themselves.

Consent for publication
Patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

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