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Whole-body magnetic resonance/diffusion-weighted sequence with background signal suppression (WB-MR/DWIBS) vs. ¹⁸F-FDG PET/CT in diagnosis of lymphoma

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Abstract

Background: The purpose of this study was to compare the performance of whole-body magnetic resonance/diffusion-weighted imaging with background signal suppression (WB-MR/DWIBS) method, with that of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT), for lesion detection and initial staging of patients with lymphoma using the histopathologically diagnosis as a reference standard.

Results: Thirty-two patients with newly pathologically proven lymphoma were enrolled in this prospective study from May 2018 to January 2020 (27 males, 5 females). All patients underwent PET/CT followed by WB-MR/DWIBS as an attempt to compare the performance of both methods for lesion detection and initial staging in patients with lymphoma.

The overall sensitivity, specificity, PPV, NPV, and accuracy of ¹⁸F-FDG-PET/CT vs WB-MR/DWIBS in correlation with reference standard data in detection of lymphoma were calculated for PET/CT 96%, 100%, 100%, 80%, and 97% while those of WB-MR/DWIBS were 93%, 76%, 96%, 61%, and 91%, respectively.

Conclusion: ¹⁸F-FDG PET/CT remains the standard reference of imaging in evaluation of lymphoma due to its higher sensitivity and specificity over WB-MR/DWIBS. Future studies with larger cohorts are necessary for better evaluation of the role of WB-MR/DWIBS in lymphoma patients. The current study highlights the potential complementary role of WB-MRI/DWIBS in the context of bone marrow involvement evaluation omitting unnecessary bone marrow biopsy.

Keywords: Lymphoma, Whole-body magnetic resonance with diffusion-weighted imaging with background signal suppression (WB-MR/DWIBS), ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT)

Background

Lymphoma is the most common primary hematopoietic malignancy which is also considered as one of the most curable forms of cancer [1]. It constitutes approximately 5% of new cancers worldwide, arising from mature or immature B cells, T cells, or natural killer cells at various stages of differentiation. Mature B cells lymphomas comprise over 90% of lymphoid neoplasm and include

Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The most common types are follicular lymphoma and diffuse large B cells lymphoma [2]. After a histopathologically diagnosis has been established, the imaging-based initial staging will influence the choice of therapy and prognosis, aid in radiation therapy planning for localized disease, and provide a baseline for treatment response monitoring. HL and NHL staging is currently based on Cotswold's modification of the Ann Arbor classification system. This system uses the number of tumor sites, the extent of involvement (nodal or

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extra-nodal), and its distribution as staging factors, whereas Cotswold's modification also take tumor burden as a complementary factor [3].

According to the biological behavior and consequently the prognosis, lymphoma can be grouped as low grade and aggressive (intermediate and high grade) tumors. The presence of extra-nodal disease has also prognostic implications as this may define a more advanced staging status (III or IV).

The accurate assessment of the initial extent of the disease determines the optimal treatment plan, and monitoring for treatment response, and guides the treatment duration and choice of therapeutic modality [4].

18-F-fluoro-2-deoxyglucose positron emission tomography (18F-FDG-PET/CT) has been advocated as the method of choice for lymphoma staging since it enables whole-body analysis with high sensitivity detection of the affected areas, as it combines the capacities for anatomical and function assessment. The principle of the imaging test is based on metabolic changes that reflect fundamental differences in the central metabolic pathways in malignant tissue. Most cancer cells exhibit elevated levels of glycolysis, and this metabolic pathway seems to be related to a higher glucose up take. As a result of those changes, tumor cells produce lactate at a higher levels compared to non-malignant tissues, even in the presence of oxygen, a phenomenon termed "aerobic glycolysis or the (Warburg effect) [5].

18F-FDG-PET/CT relies on this principle to detect foci of tumor proliferation. The level of FDG uptake can be evaluated using standardized uptake value (SUV). The SUV is the activity in the lesion measured. Higher FDG uptake values are seen in aggressive tumors compared to more indolent ones that usually show a very low glucose concentration. 18F-FDG PET/CT is the reference standard imaging modalities for patients affected by HL or aggressive NHL. However, there are some shortcomings to this technique amongst which are exposure of patients to ionizing radiation, contrast, and isotope agents [6].

Magnetic resonance imaging (MRI) has emerged as a safer non-invasive alternative for lymphoma staging, since progress in MRI technique now enables whole-body magnetic resonance with diffusion-weighted imaging with background signal suppression (WB-MR/DWIBS) as a good, radiation-free alternative. This method is based on the measurements of Brownian motion of water molecules in the biological tissue. In many pathological conditions, water diffusivity is impacted (low) due to increased neoplastic cellularity or swelling in inflammation or infectious lesions. It also concerns lymphomas, where cells are densely packed and randomly organized, inhibiting an effective motion of extracellular water. DWIBS provides cross-sectional imaging

of the entire body, with a high soft tissue contrast, and functional information [7]. The apparent diffusion coefficient (ADC) can provide useful information on treatment response and help in distinguishing benign from malignant tissues. Based on that water molecules with large degree of motion or a great diffusion distance (e.g., within the intravascular space) will show signal attenuation with small b values (e.g., $b = 50, = 100 \text{ s/mm}^2$). By contrast, the large b values (e.g., $= 1000 \text{ s/mm}^2$) are usually required to perceive slow-moving water molecules or small diffusion [8].

The purpose of this study was to compare the performance of (WB-MR/DWIBS) whole-body magnetic resonance/diffusion-weighted imaging with background signal suppression method, with that of (18F-FDG-PET/CT) 18F-fluorodeoxyglucose positron emission tomography/computed tomography for lesion detection and initial staging in patients with lymphoma using the histopathologically diagnosis as a reference standard.

Methods

Patient's selection and preparation

We enrolled in this prospective study 32 patients with newly diagnosed lymphoma of different types over a period from May 2018 to January 2020, (27 males and 5 females) with age ranged from 16 to 60 years. All patients underwent routine evaluation include history, physical examination, and blood sugar test.

Exclusion criteria were contraindications to MRI, previous diagnosis of malignancy, patients with renal function impairment (serum creatinine $> 2 \text{ mg/dL}$), patients with blood glucose level $> 160 \text{ mg/dL}$, and patients received chemotherapy prior to the initial staging or in between the two techniques.

Patients underwent 18F-FDG PET/CT and WB-MRI/DWIBS within 10 days of diagnosis and before starting the treatment. Staging was based on Ann Arbor staging system considering patients symptoms and bone marrow Biopsy (BMB).

18F-FDG-PET/CT protocol

18F-FDG-PET/CT is obtained using PET/CT scanner (Discovery STE; GE Healthcare, Boston, USA). Patient was fasted for at least 6 h before the examination. A dose of 5.5 MBq/kg 18F-FDG was injected intravenously 60 min before the scan, patients were asked to rest in a quiet room devoid of distraction to minimize physiological uptake of FDG. Diagnostic CT was performed using the following diameters, 120 kV, 350 mAs, 0.5 s tube rotation, slice thickness 5 mm, 8 mm table feed, and 3 mm incremental reconstruction. A PET emission scan was performed over several bed positions from 5 to 7 for 2 min per bed position with axial field of view of 21.6 cm per bed position and in-plane spatial resolution

of 2 mm covering the same field of view as with CT. Reconstructed trans-axial PET and CT images were fused. These are then reformed into coronal and sagittal images, and data were generated.

The maximum SUV in the volume of interest was considered as the SUV max for the purpose of analysis.

The PET/CT images were interpreted by two experienced radiology consultants (more than 5 years of experience) with inter-observer agreement.

Reports were compared to those of DWIBS. The readers were blinded to other modality results.

WB-MR/DWIBS protocol

All examinations were performed using a 1.5-T MR scanner (Achieva Philips Medical SSystem, Netherlands) Q-body coil with the patient positioned feet first to cover head, neck, and trunk. Sequences used were T1-weighted Turbo Spin Echo (TSE) and T2-weighted short T1 Inversion Recovery (STIR) in coronal orientation to encompass all anatomical districts from head to the mid-thigh.

Coronal T1-weighted and STIR and axial DWIBS sequences were performed by the following parameters. In coronal T1-weighted sequence, single-shot turbo spin echo, TR/TE shortest, slice thickness 6 mm, gap 1 mm, number of slices for station 39, FOV 350 × 265, acquisition matrix 208 × 287, reconstruction matrix 512, acquisition voxel size 1.27 × 1.85 × 6.00, reconstructed voxel size 1.04 × 1.04 × 6.00, number of acquisitions 1, acquisition time/sequence 63 s. In coronal STIR, the following parameters were used: single-shot turbo spin echo, TR/TE shortest, inversion time 165 ms, slice thickness 6 mm, gap 1 mm, number of slices for station 39, FOV 350 × 265, acquisition matrix 336 × 121, reconstruction matrix 512, acquisition voxel size 1.58 × 2.18 × 6.00, reconstructed voxel size 1.04 × 1.04 × 6.00, number of acquisition 2, acquisition time/sequence 62 s. Both T1W and STIR images were acquired in free breathing. DWIBS sequence were acquired in the axial plane, in free breathing and with the following parameters: single-shot EPI, TR/TE shortest, inversion time 180 ms, slice thickness 6 mm, gap 0 mm, number of slices for station 44, FOV 530 × 303, acquisition matrix 108 × 61, reconstructed voxel size 1.5 × 1.50 × 600, half-scan factor 0.627, EPI factor 61, *b* values 0–1000 s/mm², number of acquisition 2, acquisition time/sequence 3 min, and 29 s.

DWIBS images were reconstructed on radial (for a volumetric view) and on coronal planes, with slice thickness 4 mm, gap 1 mm, number of images 44. The reconstructed images were merged and a coronal whole-body/DWIBS images were obtained.

ADC maps were automatically generated from DW images by the MR software.

The WB-MR/DWIBS images were interpreted by two experienced radiology consultants (more than 5 years of experience) with inter-observer agreement.

Reports were compared to those of PET/CT. The readers were blinded to other modality results.

Images analysis for both modalities

For standardized comparison of the WB-MR/DWIBS and PET/CT findings, anatomical regional nodal distribution was performed into 6 nodal basins cervical, axillary, mediastinal, abdominal, pelvic, inguinal, and femoral.

Standard of reference

Histopathologically proven data as well as follow-up period of 10 months.

WB-MR/DWIBS image analysis

Visual analysis

Lymph-nodes larger than 10 mm in coronal short axis on T1WI or STIR sequences have been considered positive. In extra nodal assessment, any areas with altered signal in T1WI or STIR images showing signal intensity in DWIBS higher than surrounding tissues were considered positive for lymphoma infiltration. Signal intensity of the lesion should be equal or higher than the signal intensity from the organ with highest intensity in each station as follows: in the neck, we compared with the brain; in the chest, we compare with the bone marrow; in the abdominal region with the kidney; and in the inguinal region, with the bone marrow. A diffusely enlarged spleen (> 13 cm) without focal lesions was also considered positive.

Bone marrow infiltration was divided into focal or diffuse involvement. Focal disease was diagnosed. If there is patchy lesion with signal intensity higher than the surrounding bone marrow, the diffuse involvement was defined as wide-spread DWI signal intensity, similar to or higher than the spleen, corresponding to a hypo-intense signal in T1WI and hyper-intense signal in T2W-STIR images.

Semi-quantitative analysis

For each lymph node region and organ recorded as positive on DWI, the lesion showing the lowest signal intensity on ADC maps was identified.

18F-FDG PET/CT images analysis

Visual analysis

Any focus of elevated FDG metabolism in comparison with the liver and mediastinum, and not located in areas of normal FDG uptake, was considered positive.

PET/CT images were assessed for lymphomatous infiltration using a 5-point grading system in which the lesion uptake was compared to the liver uptake as follows:

score 0 (no uptake), score 1 (lesion uptake < liver uptake), score 2 (lesion uptake = liver uptake), score 3 (lesion uptake > liver uptake), score 4 (intensive lesion uptake that is significantly higher than liver).

Score 0 = the lesion is definitely negative, score 1 = it is probably negative, score 2 = the lesion is equivocal, score 3 = the lesion is probably positive, and score 4 = the lesion is definitely positive.

Quantitative analysis

18F-FDG PET/CT was measured by SUV max, a region of interest was manually placed on each lesion of abnormal uptake and it was calculated.

Results

This prospective study was performed on 32 patients with histopathologically proven lymphoma. Twenty-two patients were diagnosed HL and 10 B-NHL. Among B-NHL, 7 were aggressive and 3 were low grade (indolent). Patients were staged according to Ann Arbor staging system with a higher frequency of stages II and III diseases in both types of lymphoma.

A total of 320 sites (nodal and extra-nodal) have been assessed for lymphoma infiltration using combined radiological and histopathologically proven data as well as follow-up period of 10 months. Comparing with the reference standard, these lesions were divided into lymphomatous infiltration in 81 sites and free of infiltration in 239 sites. For each site, 18F-FDG-PET/CT and WB-MR/DWIBS results were correlated to the reference standard data.

As regards the 18F-FDG PET/CT, 80 lymphomatous infiltration were detected, 78 true positive sites, and 2 false-positive nodal sites. And the 240 free lymphomatous sites were 237 true-negative sites and 3 false-negative sites including one splenic and two bone marrow infiltrations which were confirmed by biopsy as shown in Table 1 (Figs. 1 and 2).

As regards the WB-MR/DWIBS, 73 involved sites were noted, 68 true-positive, and 5 false-positive lesions. The remaining 247 depicted as free sites were proved to be 243 true negative and 13 false negative as shown in Table 2.

The overall sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET/CT versus WB-MR/DWIBS in correlation with reference standard data in detection of

lymphoma were calculated for PET/CT 96%, 100%, 100%, 80%, and 97% while those of WB-MR/DWIBS were 93%, 76%, 96%, 61%, and 91%, respectively as shown in Table 3.

In attempt to explore the impact on patient's staging and further management decision, PET/CT and WB-MR/DWIBS staging accuracy was compared with the reference staging of clinico-radiological follow-up, and histopathological results are shown in Table 4.

Our results displayed the following notes:

18F-FDG PET/CT showed the following:

- Better staging of 30 patients out of 32 patients.
- False down-staging of two patients (one patient was staged IV by positive bone marrow biopsy and was missed by FDG-PET/CT, the other one was stage II having focal gastric and splenic involvement but were missed by FDG-PET/CT).
- No up-staging were noted.

WB-MR/DWIBS showed the following:

- Successfully staging of 24 patients out of 32 patients and false results of 8 patients.
- False down-staging of 4 patients (2 patients with stage III by missing splenic infiltration in average size spleen and 2 patients in stages I and II by missing nodal lesions).
- False up-staging of 4 patients (3 patients in stages II and III and one in stage O; all had false-positive splenic infiltration in large-sized spleen).

Discussion

In lymphoma staging, 18F-FDG PET/CT has been used as the most accurate method upon several imaging modalities; however, its sensitivity and specificity vary according to the histological subtype of the disease. WB-MR/DWIBS has emerged as a non-ionizing, functional, non-invasive diagnostic tool [9]. However, the unique in this study is the customized number of examined patients with initial staging and pathologically proven Hodgkin and non-Hodgkin lymphoma.

In the current study, we compared the performance of WB-MR/DWIBS and 18F-FDG PET/CT in 32 histopathologically proven lymphoma patients in diagnosis of lymphoma, assessing its impact on the staging and the therapeutic management.

The overall sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET/CT versus WB-MR/DWIBS in correlation with reference standard data in detection of lymphoma were for PET/CT 96%, 100%, 100%, 80%, and 97% while those of WB-MR/DWIBS were 93%, 76%, 96%, 61%, and 91%, respectively.

Table 1 Correlation between FDG-PET/CT and the reference data

	True-positive sites	True-negative sites	Total
FDG PET/CT+ve	78	2	80
FDG PET/CT -ve	3	237	240
Total	81	239	320

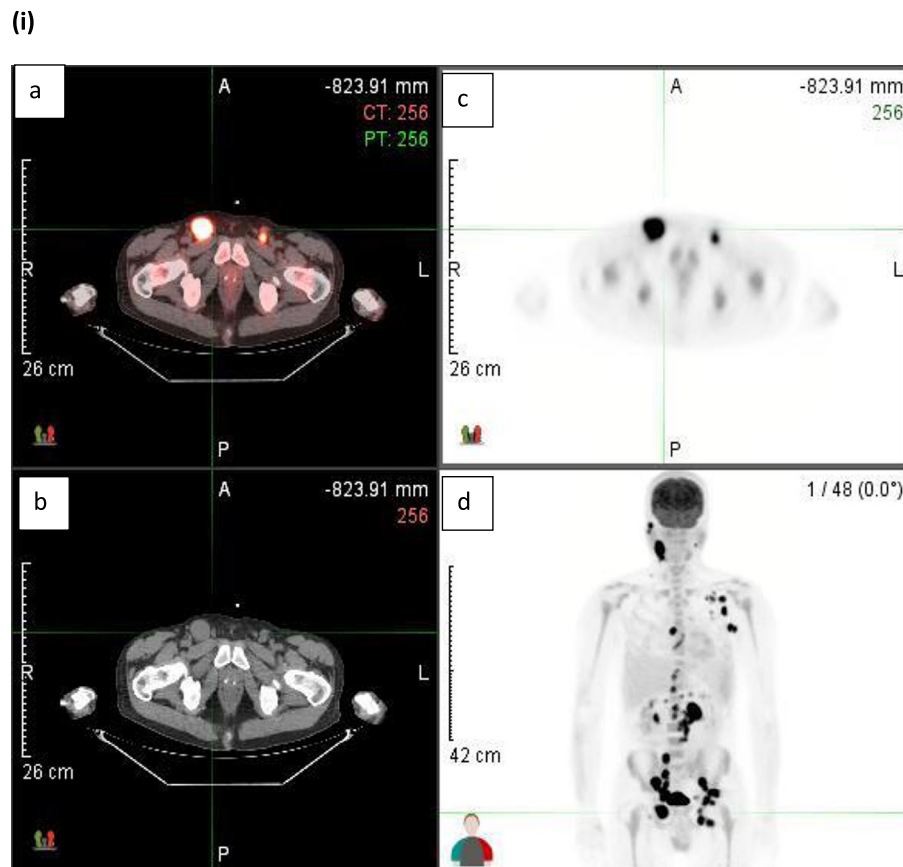


Fig. 1 A 59-year-old male with histopathologically proven lymphoma. (i) Axial PET/CT fused image (a), axial CT (b), and axial PET (c) of the inguinal region and coronal MIP PET (d) showed multi-station FDG avid lymphadenopathy consistent with lymphoma with average SUV max 12.4. (ii) Axial DWIBS (a) and ADC map (b) of the same patient showed restricted diffusion at right inguinal and right external iliac lymph nodes

As regards lymph node involvement, the current study shows no false-negative nodal sites were demonstrated by F18-FDG PET/CT in our study compared with the reference standard with sensitivity 100%. Two false-

positive inguinal nodal sites by FDG PET/CT proved to be inflammatory in nature.

These correspond with previous studies done by Cristina et al. [10], as the authors concluded that the

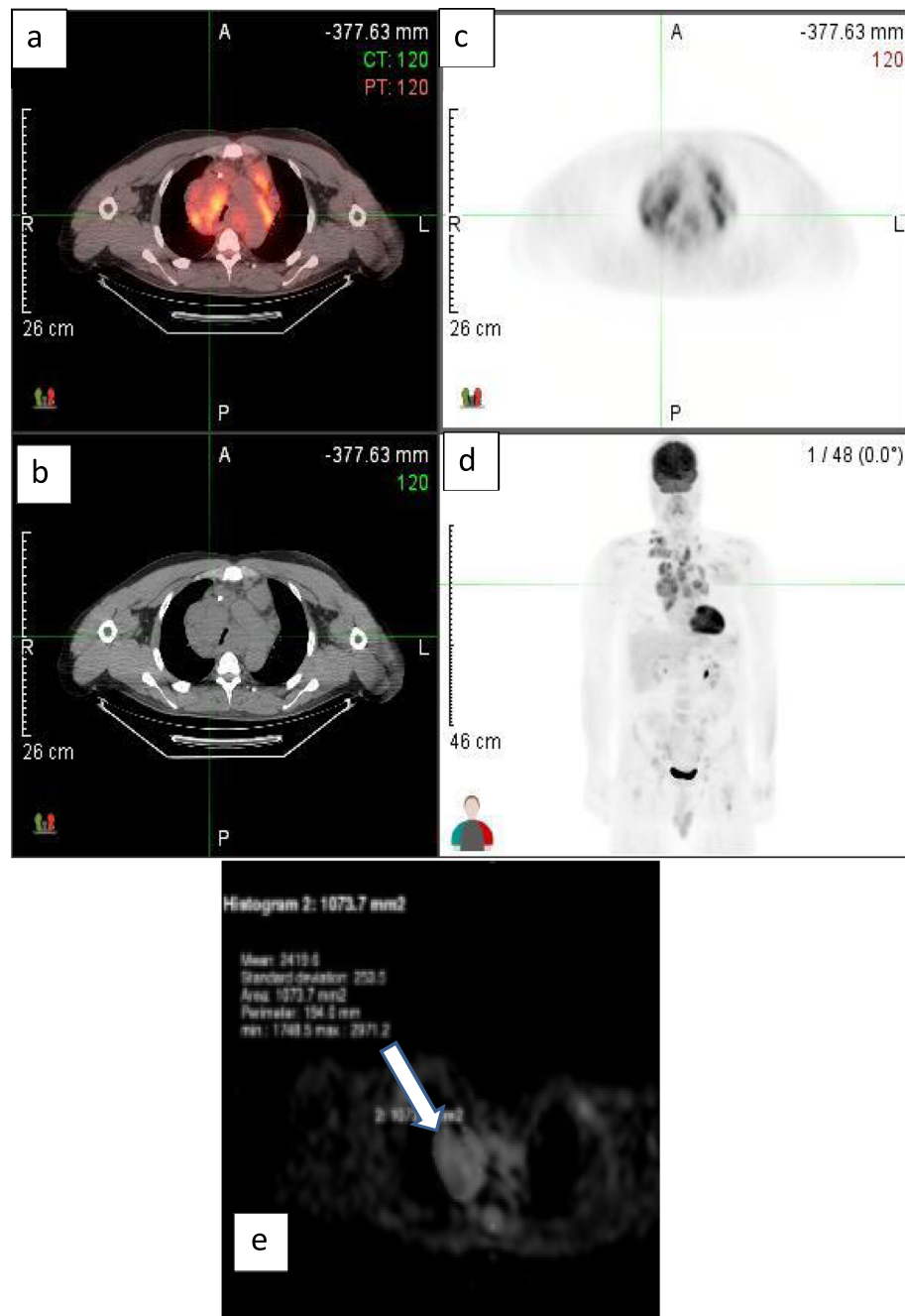


Fig. 2 A 35-year-old male with histopathologically proven lymphoma. Axial PET/CT fused image (a), axial CT (b), and axial PET (c) of the mediastinum, and coronal MIP PET (d) showed bulky FDG avid mediastinal lymphadenopathy with SUV max 5.0 producing prominent compression and displacement of the tracheal air column to the right. e Axial DWIBS/ADC map showed restricted diffusion at the mediastinal lymphadenopathy

sensitivity of FDG PET/CT in lymph node involvement had reached 100% with no false negative results, and the false-positive nodal sites were explained to be due to the avidity of FDG in inflammatory lymph node.

In the present study, the evaluation of lymph nodal infiltration by WB-MRI/DWIBS depicted one false-positive nodal lesion which could be explained by the

high-cellular density of inflammatory lymph nodes; this false-positive nodal site did not change the patient's staging. However, Van Ufford et al. [11] stated that ADC criteria may have additive value in differentiation of inflammatory from infiltrated nodes.

In our work WB-MR/DWIBS showed 11 false-negative nodal sites in 8 patients. Subsequent false down-staging

Table 2 Correlation between WB-MR/DWIBS and the reference data

	True-positive sites	True-negative sites	Total
MR-DWIBS+ve	68	5	73
MR-DWIBS -ve	13	234	247
Total	81	239	320

occurred in two patients; both patients had small-sized cervical and mediastinal lymph nodes (< 1 cm) that were both FDG avid.

This was agreed with the results of Thomas et al. [12] where they mentioned that the images' interpretation in WB-MRI/DWIBS is based on size parameter. Size criteria were the major determinant for large number of false-negative lesions. It is common opinion in the literature that the size criterion has significant limitations in any kind of tumor.

As regards the extra-nodal involvement, both methods can identify focal splenic lesions as stated by Nagham et al. [13]; however, PET/CT better evaluate the diffuse splenic involvement compared to the WB-MRI/DWIBS because the later depends on dimensional criterion.

The aforementioned conclusion is in accordance to the present results as the splenic involvement was confirmed in 8 out of the 32 patients. In respect to PET/CT, 7 out of 8 patients with splenic infiltration were confirmed, and 1 patient was missed. However, WB-MRI/DWIBS depicted 2 false-negative and 4 false-positive patients.

In the present study, bone marrow infiltrates was diagnosed in 6 out of the 32 patients. There were no false-positive patients depicted by PET/CT with specificity 100%; however, there were two false-negative patients. Regarding the WB-MRI/DWIBS, our study showed superior merits in evaluation of bone marrow infiltration with sensitivity and specificity of 100%, as the spatial

Table 3 Overall comparison between 18F-FDG-PET/CT and WB-MR/DWIBS in detection of infiltrated sites in 32 lymphoma patients

	PET/CT	DWIBS
True +ve	27	26
False +ve	0	1
True -ve	4	3
False -ve	1	2
Sensitivity	96%	93%
Specificity	100%	76%
PPV	100%	96%
NPV	80%	61%
Overall accuracy	97%	91%

Table 4 F-FDG-PET/CT and WB-MR/DWIBS staging accuracy in correlation with the reference staging

	18-FDG PET/CT		WB-MR/DWIBS	
	Patient no.	%	Patient no.	%
Accurate-staging	30	94	24	75
Up-staging	2	6	4	12.5
Down-staging	0	0	4	12.5

resolution, high contrast, and tissue differentiation are contributing factors. These results correspond with previous studies done by [14, 15].

There are merits and limitations of the current study:

First, the strength of the study includes its prospective nature for addressing a comparison between FDG PET/CT and WB-MRI/DWIBS in detection of nodal and extra nodal lymphoma as well as assessment of their impact on the management.

Its limitation included the small number of patients which were involved. Second, the study was done on heterogeneous group of patients with different pathological subtypes of lymphoma. Third, the accuracy of PET/CT and WB-MRI/DWIBS was not fully established on basis of histopathologically examination as it was not possible to confirm the diagnosis for each lymph node and extra nodal site histopathologically. Alternatively, a clinical and radiological follow-up was used. Future studies with larger cohorts are necessary for better evaluation of the role of WB-MR/DWIBS in lymphoma patients.

Conclusion

18F-FDG PET/CT remains the standard reference of imaging in evaluation of lymphoma due to its higher sensitivity and specificity over WB-MR/DWIBS. WB-MRI/DWIBS has a complementary role to PET/CT especially in the context of bone marrow involvement omitting unnecessary bone marrow biopsy.

Abbreviations

WB-MR/DWIBS: Whole-body magnetic resonance/diffusion-weighted imaging with background signal suppression; 18F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; SUV: Standard uptake value; PPV: Positive predictive value; NPV: Negative predictive value

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Duplicate publication

The manuscript is original, and it is not under consideration by any other journal.

Author's contributions

The single author is solely responsible to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. The author 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 ethics committee of October 6 University Hospital. Committee's reference number: not applicable. Consent for participation was signed for each patient.

Consent for publication

Consent for publication was signed for each patient.

Competing interests

The authors declare that they have no competing interests.

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