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Whole Body Magnetic Resonance Imaging for Staging Hodgkin Lymphoma in Adolescents

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Abstract

Background: Once a malignant lymphoma has been diagnosed, the staging of the disease must be assessed, as this determines treatment planning and prognosis as well as monitoring the effect of therapy.

Aim of Study: This study aimed at exploring the role of the whole body MRI (WB-MRI) as well as its drawbacks and limitations as an emerging whole body imaging modality and to compare between (WB-MRI) and 18F fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT), for staging adolescents' patients with pathologically proven Hodgkin lymphoma.

Material and Methods: This prospective study included 60 adolescents referred to the diagnostic radiology department with pathologically proven Hodgkin lymphoma. Their ages ranged from 12 to 18 years. Patients were seen at the radiology department from March 2017 to December 2020. History, clinical examination, conventional imaging (CT scan of the neck, chest, abdomen and pelvis) and bone marrow biopsy, which was considered the gold standard of the results were done. All patients underwent integrated 18F-FDG PET/CT then whole-body diffusion weighted imaging (DWI) within 2 days with no chemotherapy was given in-between the two examinations.

Results: In our study, taking the biopsy results and/or combined clinical /radiological findings as a standard reference, a comparison between the overall results of 18F-FDG PET/CT and WB-MRI/DWIBS was performed. We found that PET-CT had significantly higher results in the assessment of Hodgkin Lymphoma patients with statistically higher sensitivity, specificity, accuracy, PPV & NPV (98.9%, 99.5%, 98.8%, 99.5% and 99.3%) compared to (84.6%, 92%, 88.8%, 92% and 91%) for DWIBS results, respectively.

Conclusion: We concluded that 18F-FDG PET/CT remains a cornerstone in detecting Hodgkin lymphoma. WB-MRI/ DWIBS may provide a complementary tool for 18F-FDG PET CT especially for bone marrow evaluation rather than other infiltrates in Hodgkin lymphoma patients.

Key Words: *Hodgkin lymphoma – Whole body – MRI – Adolescents.*

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Introduction

HL represents 12% of all cancer cases in teens; it is the most common cancer between the ages of 15 and 19. Hodgkin lymphoma is also common in young adults and in adults older than 55 but it is very uncommon in children under age 5 **[1]**. When a malignant lymphoma diagnosed, the spread of the disease (staging) should be investigated and this affects the management plan, prognosis as well as the effect of therapy **[2]**.

Imaging with combined ([18F] FDG) positron emission tomography and (PET/CT) is considered an achievement in imaging and staging of Hodgkin lymphoma. There are, however, some shortcomings to these techniques; FDG PET/CT imparts a considerable dose of ionizing radiation and isotope agents **[3]**.

(WB-MRI) has an advantage of being a radiation-free over PET/CT in detecting anatomic and functional images together. Takahara et al., **[4]** detected a method of DWI, called DWIBS "diffusion-weighted whole-body imaging with background body signal suppression" in which a high-quality image of the whole-body was taken during breathing. WB/MRI with this new concept of DWIBS seems a feasible and promising technique for both initial staging and response assessment in patients with lymphoma **[5]**.

We aimed to detect the role of (DWIBS) MRI and to compare between it and 18Ffluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT), for staging adolescents patients with biopsy proven Hodgkin lymphoma.

Material and Methods

Technique:

An approval by the Research and Ethical Committee of Kasr El-Aini Hospital has been taken for the present study. Verbal consent had been obtained from the patients.

The study included 60 adolescent's patients (male: female=38:22); were referred to the radiology department from the oncology department. The ages were from 12-18 years, with an average age of 15.6 years, there was male predominance with male to female ratio about 1.5:1.

All patients were subjected to history taking, clinical examination, laboratory investigations [Erythrocyte sedimentation rate (ESR), Lactate dehydrogenase (LDH), complete blood cell (CBC) count studies, Serum creatinine and alkaline phosphatase (ALP)], conventional imaging (CT scan of the neck, chest, abdomen and pelvis) and bone marrow biopsy. Within 7 days from each other, Integrated FDG PET/CT and whole-body DWI were done without chemotherapy/treatment given in-between the two examinations.

Inclusion criteria:

- Patients with histo-pathologically proven lymphoma were included.
- Life expectancy <6 months.

Exclusion criteria:

- Patients with double primary malignancy.
- Patients with contraindications to MRI (such as claustrophobia and implanted pacemakers).
- Patients received chemotherapy in-between the two modalities.
- Prior chemotherapy or steroid therapy in patients coming for initial staging.
- CNS or cutaneous involvement.

I- *Integrated PET/CT:*

- *The examination technique:*

Integrated PET/CT systems (GE Medical Systems) were used in the current study. This dedicated system permitted the acquisition of co-registered CT and PET images in one session. All patients were asked to fast for six hours prior to scan. A fixed fluorodeoxyglucose dose of 5.5 MBq/Kg were given, an hour before the exam. The patient was lying comfortably with head fixation and arms up.

CT/PET Technique:

Table (1) summarizes the CT and PET protocols used in our study. Patients who gave history of contrast allergy and/or renal impairments (Renal functions were checked before examination) were not given contrast. The PET scan was performed over several bed positions. Axial, coronal and sagittal images for both techniques were first reconstructed separately, and then integrated PET and CT images were also generated.

Table (1): The CT and PET parameters used in the current study.

CT Parameters	Description	PET Parameters	Description
Kilovolt peak (kVp)	120 kVp	Number of bed positions	5-7
Milliampere-seconds (mAs)	350 mAs	Time per bed position (minutes)	2 minutes
Tube rotation time (seconds)	0.5 seconds	Axial field of view per bed position (cm)	21.6 cm
Slice thickness (mm)	5 mm	In-plane spatial resolution (mm)	2 mm
Table feed (mm)	8 mm	–	–
Incremental reconstruction (mm)	3 mm	–	–

- *PET-CT images interpretation:*

Analyses were performed by a qualified physician of radiology and a qualified physician of nuclear medicine independently with more than 15 years of experience. Both physicians were unaware of the clinical history and WB-MRI/DWIBS and BMB results.

Nodal assessment:

PET: Lymph nodes were observed positive if the flurodeoxyglucose uptake were more than the surrounding background or the mediastinal blood pool regardless of size.

CT: Positive lymph nodes were considered if their size were more than 1 cm in the long axis measurements and/or they showed loss of their normal configuration (normal oval shape and central fatty hilum).

PET-CT: Matching the level of fluorodeoxyglucose uptake with CT findings was then done and accordingly a conclusive diagnosis was decided.

Extra nodal assessment:

Focal or diffuse fluorodeoxyglucose increased uptake, higher than the surrounding background were considered positive, not including the phys-

iological uptake. Diffusely Splenic FDG uptake more than the hepatic FDG uptake were also considered positive.

II- *Whole-body DWI protocol design:*

• *Technique of the examination:*

A 1.5-T MR imaging unit (Intera, Philips medical system) was used in the current study. No contrast agents were applied.

Analyses were performed by two expert radiologists with more than 10 years of experience.

Patient position: Supine & feet-first position, including most of the body of the patients from the head to the distal thigh.

DWI Technique was done axially with the Q body coil under free breathing conditions using an EPI single-shot pulse sequence. The parameters used are summarized in Table (2). Axial images were processed on the workstation. Reconstructed coronal and sagittal planes, MIP images and volumetric views were generated for assessment.

Other pulse sequences parameters: T 1-weighted Turbo Spin Echo (TSE) and T2-weighted Short TI Inversion Recovery (STIR) were the other sequences done. Table (2) summarizes the parameters used for these pulse sequences.

Table (2): The DWI, T1 and STIR parameters used in the current study.

DWI Parameters	Description	Parameters	T1	STIR
Repetition time (TR) (ms)	8773ms	TR	466	6800
Echo time (TE)(ms)	70ms	TE	18	70
Inversion recovery (IR) (ms)	180ms	*FOV:*		
		Right/Left	530	530
		Anterior/ Posterior	265	265
		Feet/Head	224	277
Slice thickness (mm)	6mm	Slice thickness	6mm	6mm
Gap (mm)	0mm	Gap	1mm	1mm
Number of slices for station	44	–	–	–
Field of view	530x303	–	–	–

Nodal assessment:

DWI: The transverse DWI images (B-value of 1000mm^2/s) together with the MIP images were examined to determine the possible lesions. Diffusion-weighted images were used to visually detect potential nodal abnormalities, regardless the size. Positive lymph nodes were considered if their signal intensity is the same or higher than the signal intensity from the organ with highest signal intensity in each level (in the neck region it was compared to the brain, in the chest region to the bone marrow (BM), in the abdominal region to the kidneys and the BM, and in the inguinal region to the BM) [6].

Other pulse sequences: Lymph nodes were measured on the T1/STIR coronal plane. Lymph nodes larger than 10 mm in short-axis diameter were considered positive.

Extra-nodal assessment:

Any areas with restricted diffusion and altered signal in T1w or STIR were considered positive.

Brain, salivary glands, tonsils, spleen, gallbladder, adrenal glands, prostate, testes, penis, endometrium, ovaries, spinal cord, peripheral nerves, and bone marrow can exhibit restricted diffusion. Therefore, only focally increased signal intensity in these organs at DWI were considered positive [7].

A diffusely enlarged spleen (longest diameter >13cm) was considered positive even if no focal diffusion restriction were present.

BM abnormalities were divided into two categories: Focal (single or multiple lesions) and diffuse. Focal disease was diagnosed if there is focal (single or multiple) DWI restriction, altered low signal in T 1 W image and high signal intensity in STIR image compared to the surrounding BM signal intensity.

Diffuse BM abnormality was defined when widespread DWI restriction, similar to, or higher than spleen, eliciting low T1W and high STIR images [7].

Statistics:

All statistical calculations were done using computer programs SPSS 22 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA).

Data were statistically described in terms of mean ± standard deviation (± SD), median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Data like (sensitivity, specificity, positive predictive value and negative predictive value) were measured for both techniques as described by Galen [8].

A probability value (p-value) less than 0.05 was considered statistically significant.

Results

According to the pathological subtypes of the patients included 40 mixed cellularity and 20 Nodular sclerosis.

Patients were staged according to Ann Arbor staging system based on clinical examination, routine laboratory and imaging procedures. 10% were stage 0, 6.7% were stage 1, 36.7% of the patients were stage II, 23.3% were stage III and 23.3% were stage IV.

18F FDG PET/CT and MRI-DWIBS staging were compared with the clinical data and histopathological biopsies. PET-CT has successfully staged 58 patients out of the 60 patients, with false staging of two patients. Two patients with BM involvement (biopsy proven) was not detected by PET CT & considered stage III instead of stage IV. MRI-DWIBS has successfully staged 50 patients out of the 60 patients. The remaining 10 patients had false staging results. Six patients had false splenic assessment (4 false positive and 2 false negative) (Fig. 1) and 4 patients had missed nodal lesions.

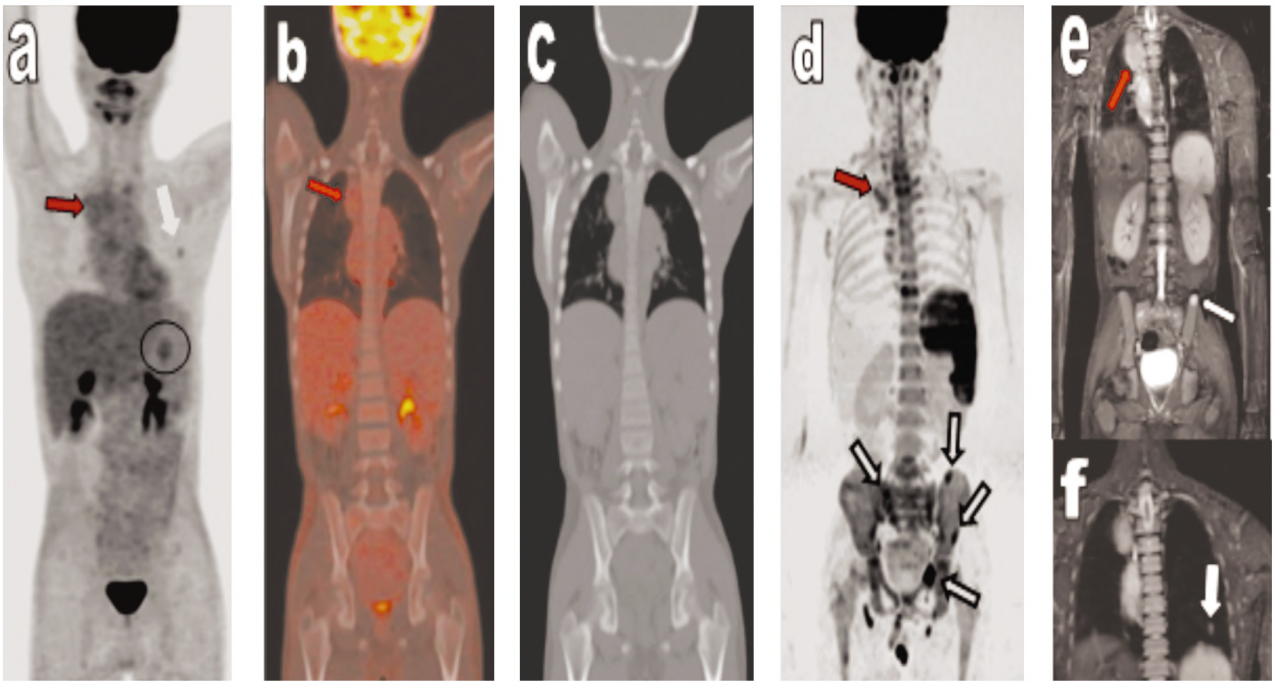

Fig. (1): PET-CT versus WB-DWIBS in a 15 years old male. (A): MIP-PET image (B): Fused coronal PET-CT images (C): coronal CT bone window image (D): Inverted grey scale MIP WB-DWIBS image. (E,F): Coronal WB-STIR images. Both PET-CT and DWIBS demonstrated positive mediastinal nodal (red arrows) and pulmonary involvement (white arrows). Multiple pelvic and vertebral osseous lesions seen at DWIBS images (open arrows), not seen in the corresponding sites at PET-CT images. Splenic involvement was diagnosed by PET-CT due to presence of metabolically active (FDG avid) focal splenic lesion (circle) and diagnosed by DWIBS due to presence of splenomegaly.

Taking the biopsy results and/or combined clinical/radiological findings as a standard reference, a comparison between the results of both techniques was performed. The sensitivity, specificity, accuracy, PPV & NPV were measured for both techniques.

According to the reference pathological data and combined clinical/radiological findings, out of 600 assessed sites in staging evaluation patients; 198 sites were positive, and 402 sites were negative.

Significantly higher sensitivity, specificity, PPV, NPV and overall accuracy of PET-CT over MRI were noticed (Table 3).

Table (3): F-18 FDG PET/CT versus MRI-DWIBS using the biopsy as a gold standard.

	PET/CT	TDWIBS1
True Positive	196	176
False Positive	2	22
True Negative	400	370
False Negative	2	32
Sensitivity	98.9%	84.6%
Specificity	99.5%	92%
PPV	98.8%	88.8%
NPV	99.5%	92%
Overall Accuracy	99.3%	91%

Regarding positive sites: Disagreement between both techniques was noted in 34 sites. Two patients BM involvement were diagnosed by MRI-DWIBS and missed by PET-CT (Fig. 2). On the other hand, PET-CT detected 32 lesions that MRI-DWIBS missed (two cervical, 12 abdominal (Figs. 3,4) and 16 mediastinal nodal lesions (Figs. 5,6) as well as 2 patients with splenic infiltration).

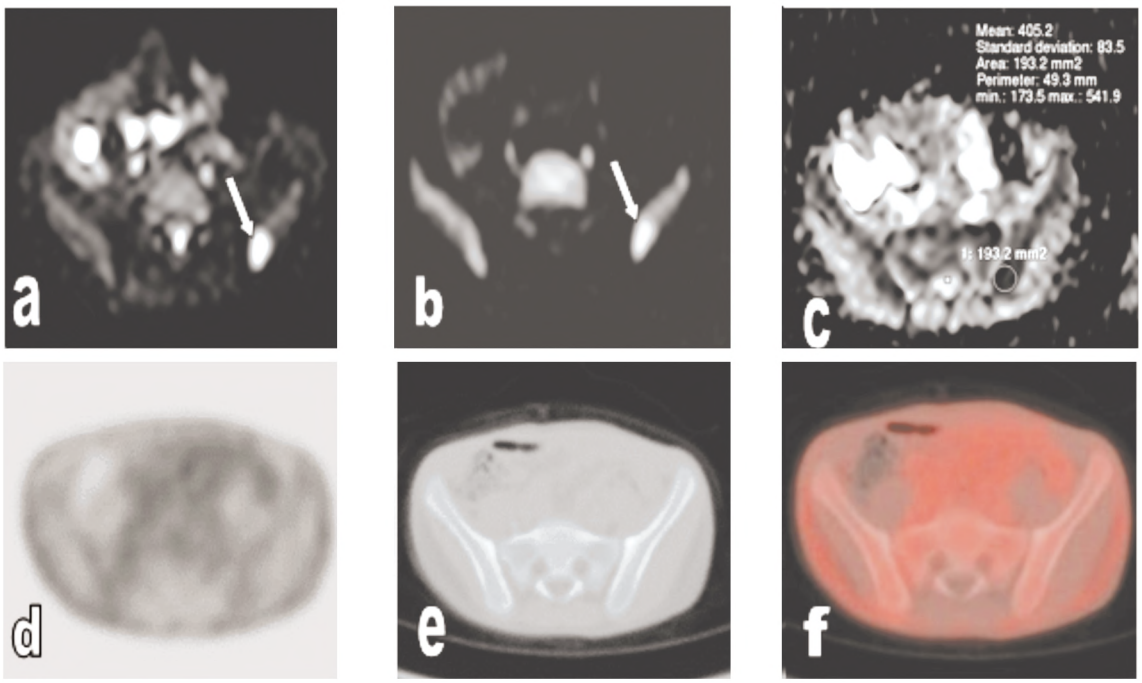

Fig. (2): Axial PET-CT versus Axial DWIBS images for the same patient: (A,B,C): Axial b0 DWI (A), b1000 DWI (B), $ADC_{=3}$ map (C). Demonstrating restricted diffusion at left iliac osseous lymphomatous lesion (arrows). ADC = 0.405 x10 mm^2/sec. (D,E,F): Axial PET (D), CT bone window (E) and Fused PET-CT (F) Images showing non visualization of the left iliac lesion with no related focal increased FDG uptake.

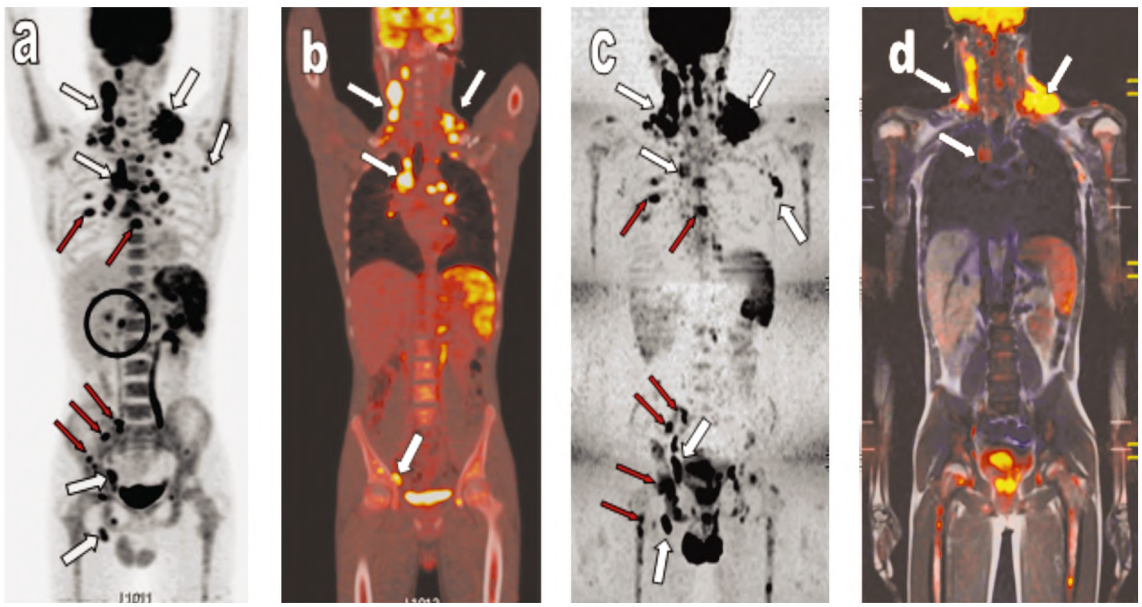

Fig. (3): PET-CT versus WB-DWIBS in 14 years old boy. (A) MIP - PET figure. (B): Fused coronal PET-CT (bone window) figure. (C): Inverted grey scale MIP WB-DWIBS image. (D): Color coded fused coronal WB-T1 and WB-DWIBS images. Both PET-CT and DWIBS demonstrated nodal involvement at cervical, left axillary mediastinal, pelvic and inguinal regions (white arrows). PET-CT demonstrated diffuse and focal splenic involvement. Splenomegaly was seen on DWIBS images, thus considered positive. Multifocal osseous (vertebral, ribs, pelvic bones, proximal femoral and proximal humeri) lesions were also demonstrated by both PET-CT and DWIBS images (red arrows). Abdominal nodal involvement was clearly seen only by PET-CT. (circle).

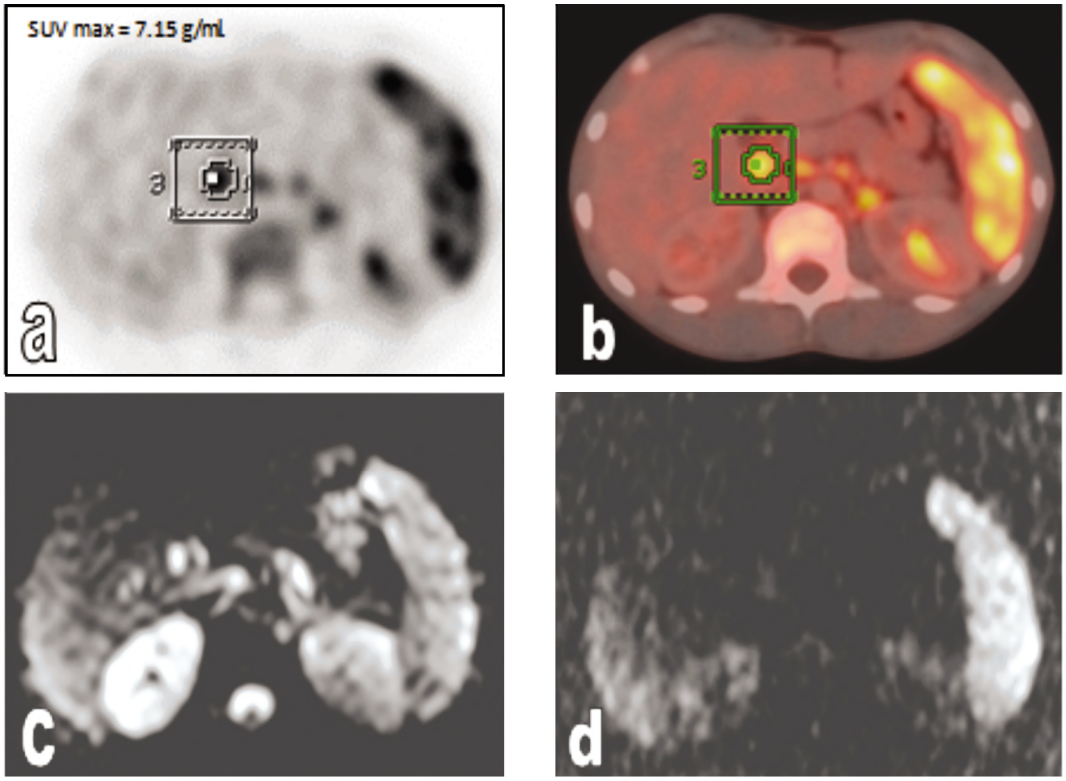

Fig. (4): Axial PET-CT versus Axial DWIBS images for the same patient in Fig. (3): (A,B): Axial PET (A) and Fused PET-CT (B) Images demonstrating multiple metabolically active (FDG avid) abdominal (porta-hepatis, peripancreatic and para-aortic lymph nodes SUV max = 7.15g/ml. (C,D): Axial b DWI (a) and b1000 DWI (b). At the same levels demonstrating no definite corresponding abdominal lymph nodes detected.

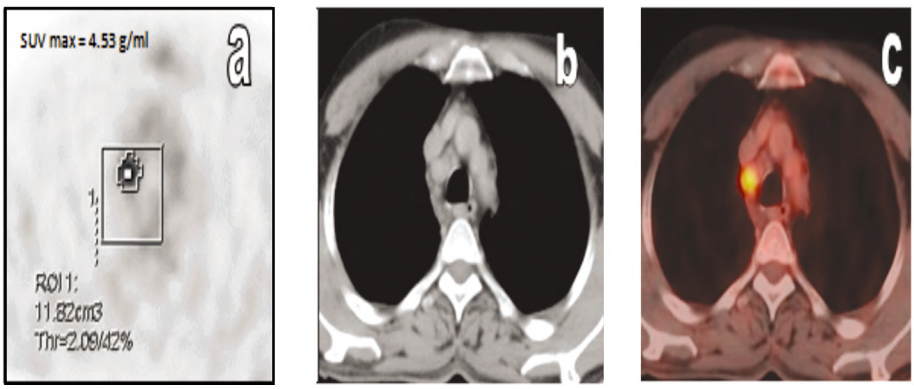

Fig. (5): Axial PET-CT images in 13 years old male: Axial PET (A), CT (B) and fused PET-CT (C) Images demonstrating metabolically active (FDG avid) right upper paratracheal (retrocaval) lymph node SUV = 4.53 g/ml.

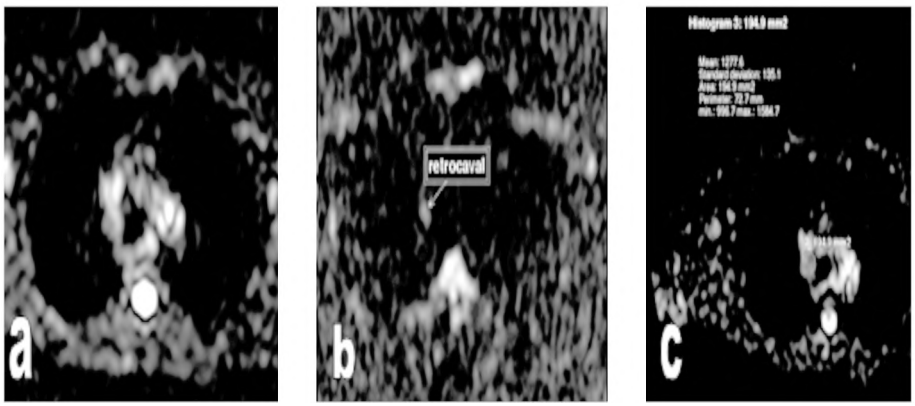

Fig. (6): Axial DWIBS images at the same level inFig. (5): (A) Axial b0 DWI (B) b1000 DWI and (C) ADC map demonstrating the retrocaval lymph node yet without restricted diffusion. ADC = 1.277 x10^{-3} mm2/sec.

Regarding negative sites: Disagreement between both methods was noted in 24 sites. PET-CT noticed two false positive inguinal lymph nodes that were negative by MRI. 22 false positive sites were depicted by WBMRI that and was negative by PET-CT (18 axillary nodal and 4 splenic).

From Table (3), we could conclude that F-18 FDG PET/CT results were clearly superior with statistically higher sensitivity, specificity, accuracy, PPV & NPV (98.9%, 99.5%, 98.8%, 99.5% and 99.3%) compared to (84.6%, 92%, 88.8%, 92% and 9 1 %) for DWIBS results, respectively.

Discussion

Hodgkin lymphoma considered one of the most common malignant lesions in adolescent. One third of Hodgkin lymphoma patients are from this age group **[9]**.

FDG-PET is a corner stone imaging technique in staging of Hodgkin lymphoma. It merges both of functional and anatomical data in a one examination and escalates high diagnostic sensitivity and specificity in HL **[10]**.

DWIBS seems a feasible and promising technique for the early staging of lymphoma that could be an additive tool to FDG-PET/CT, being a radiation free whole body imaging modality tool **[11]**.

In this study we depicted the role of the MRI/ DWIBS comparing it to 18F-FDG-PET/CT for staging adolescents' patients with pathologically proven Hodgkin lymphoma. Our study included 60 adolescents with histo-pathologically proven Hodgkin lymphoma; each was evaluated for involving nodal and extra-nodal sites using both methods.

In our study PET-CT was able to successfully stage 58 patients out of the 60 patients, with false staging of two patients, while MRI-DWIBS has successfully staged 50 patients out of the 60 patients. The remaining 10 patients had false staging results. This agreed with the study of Hampilos P., et al., **[6]**.

That showed that FDG PET/CT is the standard imaging for staging evaluation in pediatric patients with lymphoma; the high radiation dose used in PET/CT favored the use of MRI-DWIBS as a radiation-free alternative.

The overall study assessed 600 nodal and extra nodal sites for the 60 adolescents. F-18 FDG PET/ CT was superior in sensitivity, specificity, PPV, NPV and overall accuracy than MRI-DWIBS, with over all accuracy 99.3% for PET-CT compared to 91% for MRI-DWIBS.

In this study, MRI-DWI was inferior in the diagnosis of lymph nodes and spleen; there were 30 false negative nodal lesions detected by MRI-DWIBS and 2 false negative splenic lesions. Also, 18 false positive lymph nodes were detected and 4 false positive splenic lesions.

This was agreed with (Kharuzhyk S., **[13]** which detected that MRI-DW is inefficient in diagnosing spleen involvement. These results may be due to a physiological cause of restricted diffusion. The criteria of spleen involvement were stated by vertical size more than 13). The large number of false negative lymph nodes was explained by Ferrari. et al., **[14]** & Abdulqadhr G., et al., **[15]** who stated that MRI-DWIBS depends on size and the insufficiency refers to cardiac and respiratory motion which cause a drop of signal near the heart and diaphragm.

On the other hand, in the present study PET/CT was less efficient in the diagnosis of BM involvement; there were 2 false negative BM lesions as well as 2 false positive nodal lesions detected by PET/CT. Two patients with BM involvement (biopsy proven) was not detected by PET CT & considered stage III instead of stage IV, accordingly the protocol of treatment was modified.

This agreed with the study of Hugo J., **[16]** that stated that FDG PET/CT is a complementary tool to bone marrow biopsy in detecting bone marrow involvement in lymphoma patients. A negative FDG PET/CT scan cannot exclude bone marrow hyperplasia.

Conclusion:

We concluded that 18F-FDG PET/CT remains a cornerstone in detecting Hodgkin lymphoma. WB-MRI/DWIBS may provide a complementary tool for 18F-FDG PET CT especially for bone marrow evaluation rather than other infiltrates in Hodgkin lymphoma patients.

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التصوير بالرنين المغناطيسى للجسم كله لتنظيم سرطان الغدد الليمفاوية فى المراهقين

يجب تقييم سرطان الغدد الليمفاوية الخبيثة من الناحية النسيجية بمجرد تشخيصه، لأن هذا يحدد تخطيط العلاج ومراقبة تأثيره.

تهدف هذه الدراسة إلى استكشاف دور التصوير بالرنين المغناطيسى للجسم بأكمله وكذلك عيوبه والمقارنة بينه وبين التصوير المقطعى لانبعاثات البوزيترون/التصوير المقطعى المحوسب، لتنظيم المراهقين الذين يعانون من سرطان الغدد الليمفاوية.

وشملت هذه الدراسة المرتقبة ٦٠ مراهقاً أحيلوا إلى قسم الأشعة التشخيصية مع سرطان الغدد الليمفاوية الذى ثبت مرضياً. وتراوحت أعمارهم بين ١٢ و ١٨ سنة. تم رؤية المرضى فى قسم الأشعة فى الفترة من مارس ٢٠١٧ إلى ديسمبر ٢٠٢٠. تم اعتبار التاريخ المرضى والفحص السريرى والتصوير التقليدى. (التصوير المقطعى للرقبة والصدر والبطن والحوض) وخزعة نخاع العظم المعيار الذهبى للنتائج. خضع جميع المرضى لتصوير متكامل فى غضون يومين دون أى علاج كيميائى تم إعطاؤه بين الفحصين.

فى دراستنا، مع أخذ نتائج الخزعة و/أو النتائج السريرية الإشعاعية مجتمعة كمرجع قياسى، تم إجراء مقارنة بين النتائج الإجمالية لسرطان الغدد الليمفاوية.

وخلصنا إلى أن التصوير المقطعى لإنبعاثات البوزيترون/التصوير المقطعى المحوسب لا يزال حجر الزاوية فى الكشف عن سرطان الغدد الليمفاوية. قد يكون التصوير بالرنين المغناطيسى أداة للجسم بأكمله أداة تكميلية للتصوير المقطعى لانبعاثات البوزيترون التصوير المقعطى المحوسب خاصة لتقييم نخاع العظام.