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ORIGINAL ARTICLE

Role of Fluorine 18 Fluorodeoxy-Glucose (FDG) Positron Emission Tomography (PET)/ Computed Tomography (CT) in Evaluation of Lymphoma Patients

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ABSTRACT

Background: Malignant lymphoma is considered the most common hematological malignancy. Lymphoma is divided into Hodgkin's disease and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma forms most cases with more affinity to involve extra-nodal sites. The objective of the study was to highlight the role of 18F-FDG Positron Emission Tomography (PET)/ Computed tomography (CT) in evaluation & follow up cases of Lymphoma.
Methods: This prospective study was performed from January-2021 to May-2022 for staging and therapeutic assessment of lymphoma. Biopsy results were the gold standard, which compared with CT and PET/CT results.
Results: Out of 48 cases in our study came for initial staging, assessment of treatment and follow up. PET/CT showed the same results as CT in 28 cases with no changes, while 20 cases showed discordant results with CT, mostly showing changes in FDG uptake of previously noted lesions in follow up patients, which was statistically significant. PET-CT detected additional extra nodal involvement than CT in 15 cases: 6 cases splenic infiltration, 3 bone marrow and musculoskeletal lesions, 2 hepatic, 1 gastric, 1 nasal, 1 CNS and 1 breast lesion. **Conclusions:** The present findings revealed the significance of 18F-FDGPET/CT as a potential method in lymphoma initial staging. PET/CT had remarkable indications in evaluation of treatment feedback as compared to conventional CT. PET/CT is highly specific and permits definite localization of remanent masses and detects active tumor within residual mass. PET/CT was also helpful in detection of early relapsing lymphomas in both HD and NHL.

Keywords: Lymphoma, CT, PET/CT, 18F-FDG.

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INTRODUCTION

Malignant Lymphoma with an evaluated 580,590 new patients and 268,724 deaths in 2018, it comes tenth and twelfth most common cancer in males and females worldwide, respectively [1].

There are numerous lymphoma subtypes. Non-Hodgkin lymphoma (NHL) (90 percent of cases) and Hodgkin lymphoma (HL) are the two most common types of lymphoma (10 percent of cases). Multiple myeloma and immunoproliferative disorders are two other kinds of lymphoma recognized by the World Health Organization [2]. Although lymphoma can cause different signs & symptoms like weight loss, fatigue, chills & frequent infection, most patients are presented with lump or a swelling that hasn't gone away, as lymphoma causes lymph nodes to enlarge. Enlarged lymph nodes close to the surface of the body (such as side of the neck) may be seen or felt as lumps under the skin which are usually not painful [3]. Treatment of lymphoma varies according to its type; it includes one or more of the following: chemotherapy, radiotherapy, and surgery. Plasma pheresis is used to eliminate excess protein from the blood in some non-Hodgkin lymphomas due to the higher protein levels secreted by the lymphoma cells [4].

With many imaging modalities that can describe the morphological changes in lymph nodes, it's almost exclusive for the PET/CT to describe the biological changes in those lymph nodes through their uptake of FDG which has a great value in determining whether those lymph nodes are

affected or not, which in turn will have crucial role in management and treatment plan [5].

After confirming diagnosis by lymph node biopsy, PET/CT scan is very supportive in staging of the disease by scanning the whole body searching for diseased lymph nodes [6].

What gives PET/CT scan the upper hand is that it acts on the biological level of the cells which permit early discovering of the affected lymph nodes, much earlier than standard C.T or MRI scan [7]. The role of PET/CT scan doesn't end after treatment as it has major role in follow up for early observation of any suspicious lymph nodes which is very important in improving out-come result [8]. The aim of our study was to highlight the role of FDG PET/CT in assessment and follow up of cases of Lymphoma.

METHODS

This prospective study was performed at Nasser Institute for research and treatment Hospital from January 2021 to May 2022 for staging and therapeutic assessment of lymphoma. Biopsy and histopathology results were the gold standard to which we compared the CT and PET results. The Institutional Review Board at Zagazig University's Medical Faculty approved the study after acquiring signed consent from all participants (IRB approval number 6590). According to the Declaration of Helsinki, a global rule of ethics for human research, the study was conducted in line with the guidelines.

Inclusion criteria: All pathologically proven lymphoma patients.

Exclusion criteria: The cases with these criteria were eliminated from the study: cases with pregnancy, elevated blood glucose level above 200 mg/dl, Inadequate PET/CT images due to artifacts, radiotherapy within less than 3 months, chemotherapy within less than 3 weeks, and non-Cooperative Patient.

Imaging*:* The GE Discovery 690 scanner and the Bio-graph true point scanner (Siemens) were used to perform the exams and collect the data. These specialized systems combine a PET scanner with multi-section helical CT scanners, allowing for simultaneous capture of cross CT and PET images.

Patient Preparation: Just before the exam, all cases were requested to fast for 6 hours. The patients' metallic possessions were taken away. Before the exam, subjects were advised to empty their bladder. Routine random blood glucose was measured for all patients to ensure that their blood glucose value was within limits. The patient's arm was implanted with intravenous cannula for the delivery of 18F-FDG. To prevent FDG uptake in muscle, the cases were urged to limit any intense movement before testing and after radioisotope injection. They were also asked to void before scanning.

Dosage Administration: A 10 -20mCi (370 MBq; approximate dose to patient, 3-5MBq/Kg) dose of 18F-FDG was injected (45–90 min) prior to assessment. Cases were advised to be in a calm, distraction-free environment and to reduce their movements, even talking, to a bare minimum. This reduces physiologic FDG uptake into muscle, which may skew the scan results. Cases should feel comfortable.

CT Technique: The Cases were positioned in a comfortable head fixation with arms up. Scanning commenced at the level of the skull base and extended caudally to the upper thighs in a typical PET-CT whole-body study (neck, chest, belly, and pelvis). The patient was asked to breathe quietly during the study. Collimation width of 5.0 mm, pitch of 1.5, gantry rotation time of 0.8 second, and field of view of 50 cm are the scanning specifications. At one mm intervals, the helical data is retrospectively rebuilt.

PET Technique: Without moving, a PET scan was performed after the CT scan. In the 3D acquisition mode, about six to seven bed positions are scheduled for examination of the complete case with 3–5-minute analysis at each bed position.

PET/CT Fusion: Many trans-axial CT and PET pictures were initially reassembled. To make image interpretation easier, these are then converted into coronal and sagittal pictures. Fusion pictures were created that combined the two forms of data for each collection of CT and PET scans. For attenuation correction, PET image data collection was rebuilt by CT data, and co-registered pictures were shown utilizing software.

PET/CT Interpretation: All pictures were independently evaluated by a radiologist and nuclear medicine physician consultant with at least 5 years of experience as a consultant. The merged images were assessed after each study was reviewed separately.

Statistical analysis:

The data were collected and analyzed using SPSS software (IBM, Version 20.0). For characterization of quantitative data (IQR), mean, range, median, and standard deviation were used. And for categorical variables the Chi-square test was utilized. Monte Carlo correction was used for correction of chi-square when more than 20% of the cells have expected count less than 5. Kappa (κ) was used for the agreement between Pathology with CT and PET/CT. McNemar and Marginal Homogeneity Test was used to detect the significance between the different stages.

RESULTS

Patients in the studied group were 32 cases NHL (67%), and 16 cases HL (33%). 42% of cases were aged between 35 and 49 years, 36% were between 20 and 34 years, and 23% were between 5 and 65 years**.**

The patients were divided in to 3 groups according to the indication of PET/CT examination: Group A (initial staging, 12 cases), Group B (Assessment of response during treatment, 18 cases) and Group C (follow up 6 months after treatment, 18 cases), **(Fig. 1)**.
Regarding the Ann Arbor classification of HL and NHL, the cases were staged as follows: CT depicted 2 cases for each stage I, III, and IV, and 6 cases with stage II. PET/CT depicted patient in stage I, 3 patients in both stage II and III, 5 patients in stage VI **(Table 1).**

Assessment during course of treatment, CT detected progression in 8 cases, partial regression in 3 cases, complete regression in 2 cases, 5 cases in stationary course. On the other hand, PET/CT revealed progression in 13 patients, two patients with partial regression, one patient with stationary course, and complete regression in 2 patients **(Table 1)**.

Concerning follow up CT, 6 patients were identified with partial regression, 6 patients with complete regression, two patients with relapse, and 4 patients with stationary course. PET/CT showed disease relapse in 13 patients, and complete regression in 5 cases, **(Table 1).**

PET/CTshowed the same results as CT in 7 cases with no changes, while 11 cases showed discordant results with CT, mostly showing changes in FDG uptake of previously noted lesion rather than their size, which was statistically significant **(Table 2).**

Out of 48 cases in our study came for initial staging, evaluation of follow up and treatment. PET/CT detected additional extra nodal involvement than CT in 15 cases as: splenic infiltration in 6 cases, bone marrow and musculoskeletal infiltration in 3 cases, hepatic involvement in 2 case, gastric mucosa infiltration, CNS, breast involvement, and nasal infiltration in 1 case **(Fig. 2-5)**.

PET/CT showed higher sensitivity and specificity than CT as follow: CT had specificity and sensitivity of 78%, 78 % respectively with PPV of 94 % and NPV of 47 %. PET/CT had sensitivity and specificity of 100 %, 83% respectively with PPV of 95% and NPV of 100% **(Table 3).**

Table 1: Initial staging, follow up during course of treatment and follow up 6 months after end of chemotherapy by CT VS PET/CT

Initial Staging by CT VS PET/CT				
Stage	**CT**	**PET/CT**		
I	2	1		
II	6	3		
III	2	3		
IV	2	5		
Total	12	12		
Follow up during course of treatment				
	CT	**PET/CT**	**MH**	**P value**
Complete regression	2	2	17	0.034
Partial regression	3	2		
Stationary	5	1		
Progression	8	13		
Total	18	18		
MH: Marginal Homogeneity Test, p: p value for comparing between CT and PET/CT, *: Statistically significant at p ≤ 0.05.				
Follow up 6 months after the end of chemotherapy by CT and PET/CT				
	Frequency	**Percentage**		
CT				
Complete regression	6	33		

Partial regression	6	33
Stationary	4	22
Relapse	2	12
Total	18	100
PET/CT		
Complete regression	5	28
Disease relapse	13	72
Total	18	100%

Table 2: Follow up PET/CT in relation to CT

	CT		PET/CT		MH	P value
	No.	%	No.	%		
Partial Regression	6	33.3	0	0	4.637	0.001*
Complete Regression	6	33.3	5	27.8		
Relapse	2	11.1	13	72.2		
Stationary	4	22.2	0	0		
Total	18	100	18	100		
MH: Marginal Homogeneity Test, p: p value for comparing between CT and PET/CT, *: Statistically significant at p ≤ 0.05.						

Table 3: Sensitivity and specificity of PET/CT and CT

	CT	PET/CT
PPV	94%	95%
NPV	47%	100%
Sensitivity	78%	100%
Specificity	78%	83%
PPV: Positive predictive value, NPV: Negative predictive value.		

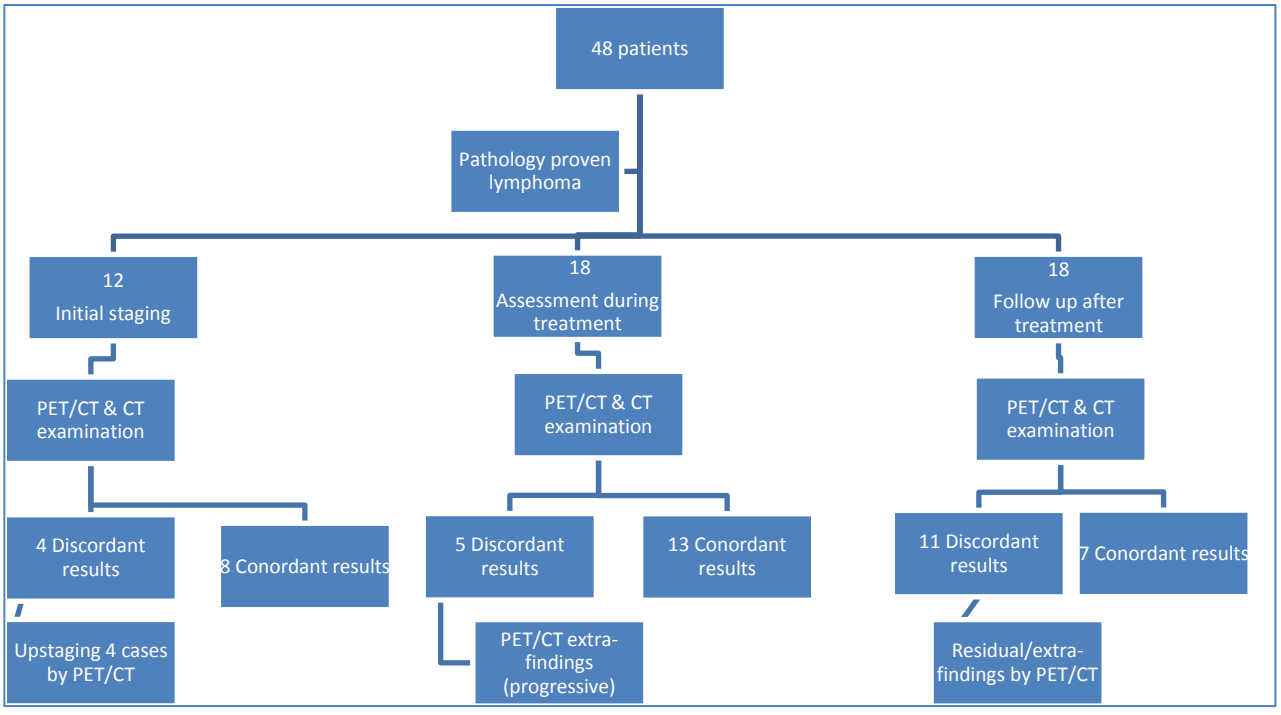

Fig. 1: Flow chart of the study group (48 patients).

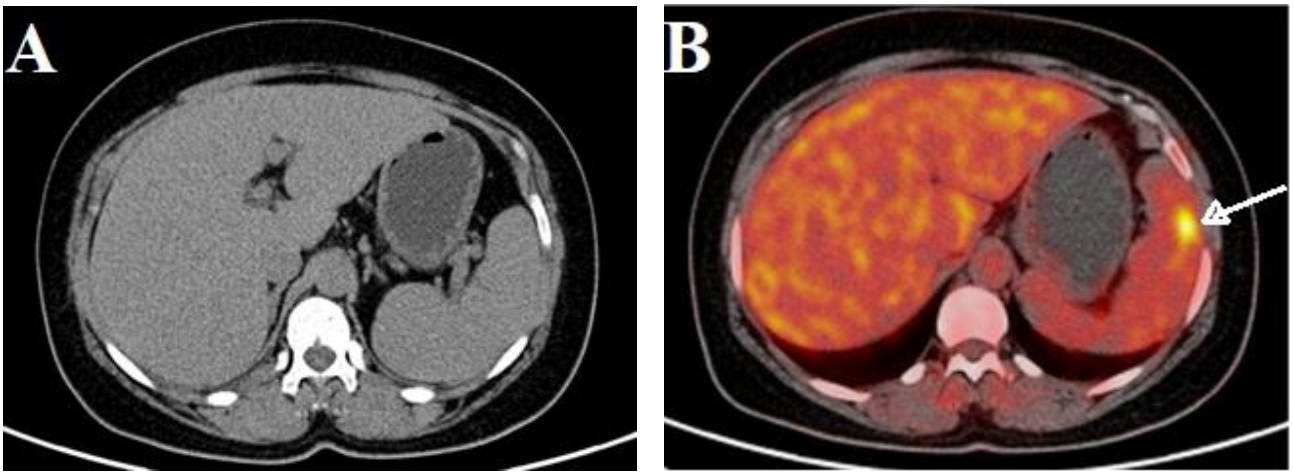

Fig.2: 61 years old female patient presented with neck swelling, (A) axial CT image of abdomen shows average size spleen, no definite focal lesion. (B) axial fused PET/CT image shows splenic focal lesion (arrow) with increased FDG uptake with SUV $_{max}$ 37. Diagnosed as HD (Mixed Cellularity), proved histopathologically with biopsy.

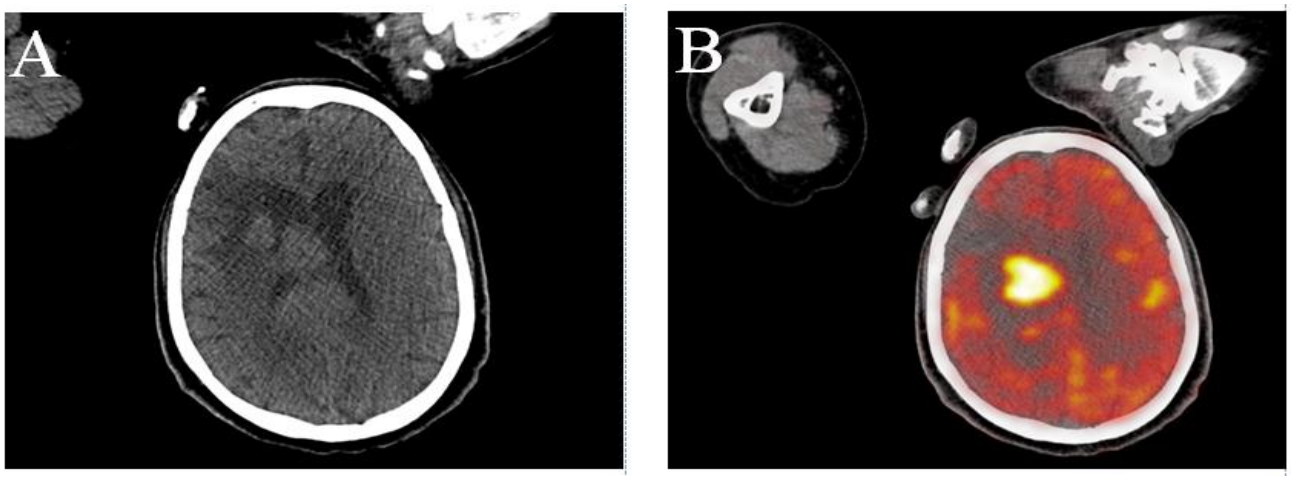

Fig. 3: 61 years old male patient presented with headache. (A) axial CT brain image shows high fronto-parietal S.O.L. (B) axial fused PET/CT image shows increased FDG uptake of the right fronto-parietal S.O.L with SUV $_{max}$ of 37. Diagnosed as NHL, proved histopathologically with biopsy.

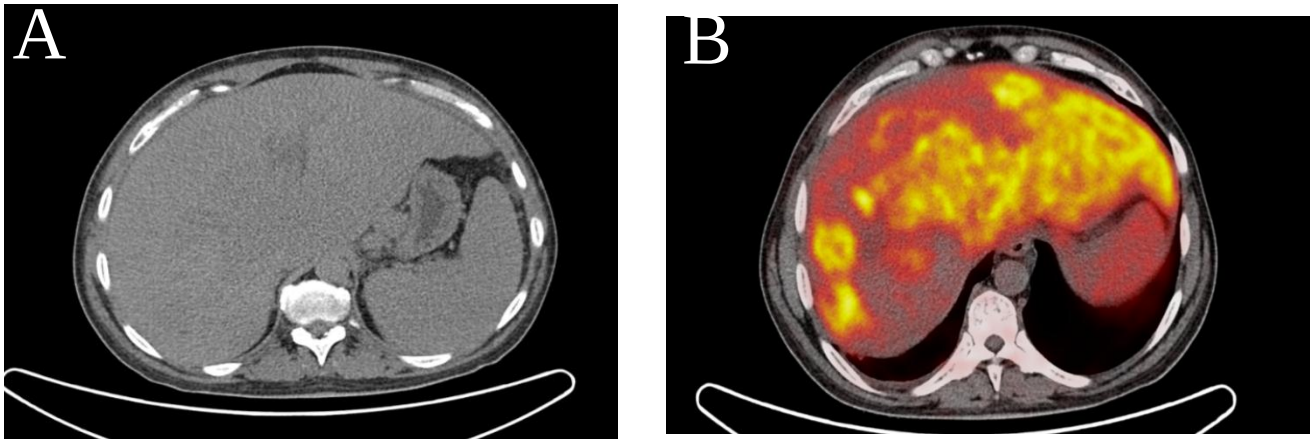

Fig. 4: 52 years old male patient presented with abdominal pain. (A) axial CT image shows enlarged liver, no definite focal lesion (B) axial fused PET/CT image shows extra-nodal involvement of liver with increased FDG uptake with SUV $_{max}$ of 43. Diagnosed as NHL (DLBCL), proved histopathologically with biopsy

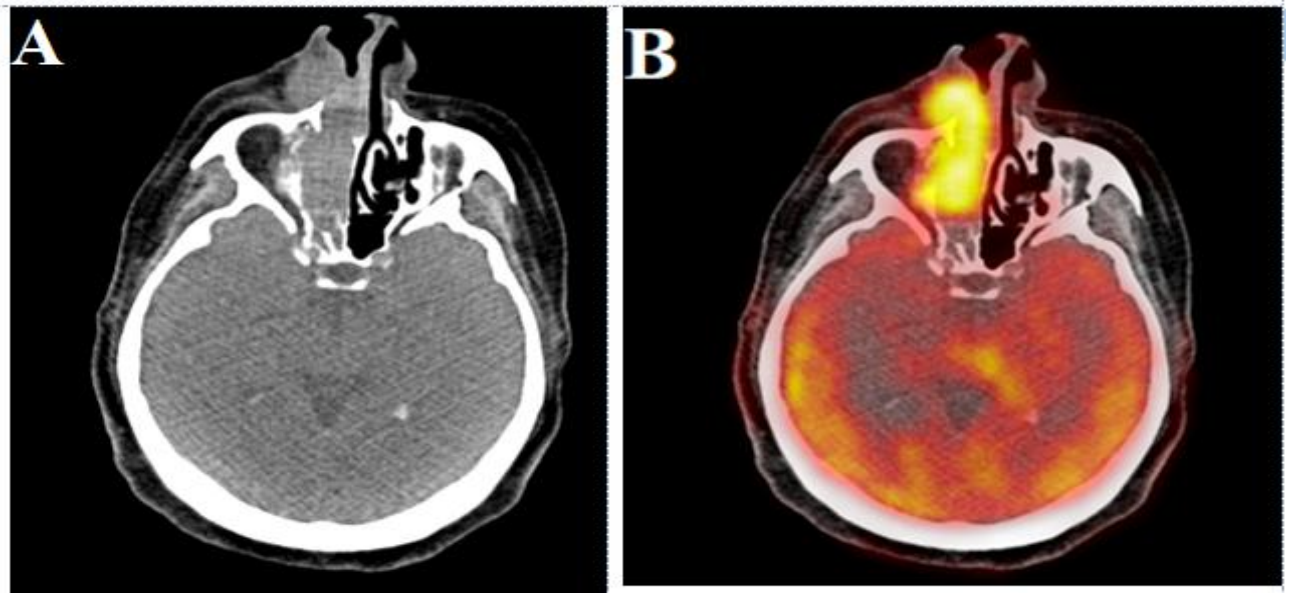

Fig. 5: 65 years old female patient presented with frontal headache, (A) axial CT image of the paranasal sinuses shows opacification of right nasal cavity by soft tissue attenuation lesion, (B) axial fused PET/CT image shows RT nasal infiltration by soft tissue mass lesion with SUV_{max} of 21. Diagnosed as NHL (DLBCL), proved histopathologically with biopsy

DISCUSSION

PET/CT has been utilized in cases with HD and NHL for staging, evaluating treatment feedback, and observing recurrence. CT, on the other hand, has inadequate sensitivity when it comes to revealing lymphomatous infiltration of bone marrow, normal-sized lymph nodes, and spleen[9]. Our study included 48 cases, 20 males (41.7%) and 28 females (58.3%), with age between 20 and 65 years. There were no remarkable variations in results regarding age and gender.

Out of 48 patients in our study group there were 32 cases NHL (67%) and 16 cases HD (33%). The most represented HD subtypes were nodular sclerosis and mixed cellularity. The most represented NHL subtypes in study group were follicular lymphoma and Large B-cell lymphoma (LBCL). Patients in our study were divided into 3 groups according to the indication of PET/CT examination: Group A (initial staging), Group B (Assessment of response during treatment) and Group C (follow up 6 months after treatment).

In our study 12 cases came for initial staging (proved lymphoma by histopathological biopsy), CT depicted 2 cases for each stage (I), (III), and (IV), and 6 cases with stage (II). PET/CT depicted 1 case in stage (I), 3 cases in both stage (II) and (III), 5 cases in stage (VI). PET/CT and CT were consistence in staging of 8 patients while PET/CT was discordant with CT in primary staging of cases resulting in upstaging of those patients from stage (I) and (II) to stage (III) and (IV) in both HD and NHL, matching with Riad et al, who detected discordant between CT and PET/CT in 26.8% of cases [10].

The added usefulness of PET/CT in the current investigation was not in revealing active sub-centimetric lymph nodes, but in identifying extra-nodal locations of illness that were missed by CT alone. The upstaged cases were as follows, two cases showed extra-nodal involvement at liver, another case showed musculoskeletal involvement, last case showed breast and lumbar involvement. The main strength of PET/CT over CT in our study was in the higher affinity to detect extra-nodal involvement. Behairy et al, conducted study on 50 patients, CT revealed 34 patients in stage I, stage II with 13 cases and stage IIE with 3 cases, while PET/CT showed 31, 2, 11, 4 and 2 in stage I, IE, II, IIE and IV respectively. Therefore, PET/CT was discordant with CT in the primary staging of 5 cases (10%). PET/CT upstaged 2 patients from stage (I) to stage (IE) due to the detection of extra- nodal pleural disease site, 1 patient from stage (II) to (IIE), 2 patients were elevated from stage (I), and (II) to (IV) [11].

Le Dortz et al, declared that PET/CT detected more additional lesions than CT scan, both nodal involvement (+51%) and extra-nodal involvement (+89%) such as osteo-medullar and splenic involvement, initial PET/CT examination changed staging in 18% of patients, especially for cases considered to have localized stage [12].

The presence of an image abnormality on a CT scan is not a reliable sign of active disease. Because CT alone cannot distinguish between viable and non-viable illness, remaining abnormalities exist in roughly 30-60% of patients following treatment. These abnormalities are commonly classified as persistent lymphoma. Only 10-20% of the remanent lumps detected at the end of treatment were positive for lymphoma on biopsy, and roughly 18% of these will return [13].

A PET/CT potential advantage is the capability to find active tumor in remnant lesions in HD and NHL. Residual mass is not uncommon finding, which is assumed as clinical obstacle in HD and moderate/high grade NHL restaging. PET/CT is more reliable in differentiation between fibrosis and viable tumor, as fibrosis doesn't have high metabolic activity, unlike viable residual tumor [14].

In our study, out of 18 cases presented for assessment of response during treatment, PET/CT and CT were consistent in 13 cases and discordant in 5 cases, detailed as follow: CT found progression in 8 cases, complete resolution in 2 patients, stationary course in 5 patients, and partial regression in 3 patients, while PET/CT found progression in 13 cases, complete resolution in 2 patients, stationary course in 1 patient and partial regression in 2 patients.

Some cases showed residual mediastinal mass which is not uncommon finding, where CT alone couldn't detect viable from non-viable tissue in those masses, PET/CT was capable of easily differentiate between viable neoplastic recurrence (increased FDG uptake) from non-viable fibrosis (non FDG avid).

Riad et al, assessed early chemotherapy feedback in their study on 51 patients PET/CT and CT were consistent in 34 cases of which 29 patients show complete regression and 5 cases still show sites of active disease. Results were discordant in 17 cases out of 51, 15 cases were false positive in CT while in PET/CT were true negative showing total remission. The remaining 2 cases, one of them shows active nodal uptake (true positive in PET/CT) in normal size lymph node which was pathologically proven later as lymphoma, the other case, PET/CT was false positive in detecting diffuse hypermetabolism in bowel which was pathologically proven to be inflammatory process not lymphomatous infiltration[10].

Whereas the total recurrence rate is modest, especially in HD, the global tendency toward less harsh therapy regimens may result in arise in relapses frequency. The accessibility of effective treatments could justify rigorous monitoring of cases at risk of relapse utilizing precise technology [15].

In our study 18 cases presented for follow up after treatment, out of 18 cases CT revealed partial regression and complete regression in 6 patients, 2 patients with relapse, and 4 cases with stationary course, while PET/CT found disease relapse in 13 cases and complete regression in 5 cases. There were remarkable findings in follow up after treatment (P value= 0.001). Riad et al, assessed 18 cases for follow up after treatment and found consistence between PET/CT and CT in 13 cases, 5cases were true positive, and8 cases were true negative in both PET/CT and CT, while discordance was only in 5 cases [10].

In our study CT had over all sensitivity and specificity of 78 %, 78 %, respectively with PPV of 94 % and NPV of 47 %, while PET/CT had over all specificity and sensitivity of 83 % and100% respectively with PPV of 95% and NPV of 100%.

Our results were comparable with Riad et al, who showed that sensitivity, specificity, PPV and NPV of 83%, 66.6%, 25%, 96.7% respectively for CT and 100%, 97.7%, 85.7%, 100% respectively for PET/CT [10].

Schaefer et al, on their study of sixty cases with HD and NHL, found out that PET/CT specificity and sensitivity was 100%, 94% respectively, while CT showed specificity and sensitivity of 86%, 88% respectively. Schaefer et al, concluded that PET/CT has higher specificity and sensitivity than CT [16].

In our investigation, PET/CT had higher specificity and sensitivity than CT, which was consistent with the findings of other previous studies. The key privilege of PET/CT over CT was its capacity to exclude active disease as well as detect relapse spots earlier.

Although PET/CT could detect additional number of sub-centimetric FDG avid lymph nodes than CT alone, yet it wasn't significant in all cases because of the associated larger sized lymph nodes either in the same or different groups that also has been detected by CT, hence no change in staging or treatment regimen.

On contrary PET/CT can detect extra-nodal additional findings that weren't detected in CT only. In our study 15 cases showed additional extra-nodal findings on PET/CT that weren't detected on CT alone as follow: 6 splenic, 3 musculoskeletal, 2 cases with liver involvement, 1 stomach, 1 nose, 1 CNS and 1 breast.

Our study had some limitations; the sample size was small due to the high cost of the technique and sufficient follow-up of cases was not accomplished to associate our results with the patients' progression-free survival or overall survival; so multicenter study and research group teamwork using a larger number of cases is required to gain more accurate outcomes.

CONCLUSION

The present findings revealed the significance of 18F-FDG PET/CT as a potential method in lymphoma initial staging. PET/CT had remarkable indications in early and delayed evaluation of treatment feedback as compared to conventional CT.PET/CT is highly specific and permits for definite depiction, localization of remanent masses and detects viable active tumor within residual mass. PET/CT was also helpful in identifying early relapsing lymphomas in both HD and NHL.

Conflict of interest: None.

Financial Disclosures: None.

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