Role of 18F-FDG PET/CT in the Assessment of Extranodal Lesions in Patients with Lymphoma: An Observational Study

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Abstract:

Background: The diagnosis and management of lymphoma require a combination of various investigations to accurately identify the subtype, stage, and prognosis of the cancer. One of the most crucial initial investigations for lymphoma is imaging studies such as computed tomography (CT) and positron emission tomography (PET) scans, which can help to identify the location, size, and extent of lymph node involvement, as well as detect any extranodal spread.
Methods: This was an observational study that investigated the results and assessment of PETCT scans performed on lymphoma patients with initial extra-nodal lymphoma or extranodal involvement of advanced nodal lymphomas. This study was conducted in Assiut University Hospital, the Nuclear Medicine Unit.
Results: A total of 112 patients were included in the analysis. Their median age was 40 (2-86) years and more than half of the participants (54.5%) were males. Primary extranodal disease was seen in 37.5% while secondary extranodal pattern was 62.5%. The site of the primary lesion was cervical lymph nodes in 82 (52.6%), followed by mediastinal lymph nodes in 19 (12.2%) and the rarest sites of primary lymphoma lesions were at the orbit, nose, skin, and prostate. The McNemar test was found to have a significant difference in the probability of detecting lesions between CT and PET/CT in bone marrow (P = 0.000), lung nodules (P = 0.000), mediastinal (P = 0.01) and para-aortic nodes (P = 0.006).
Conclusion: PET/CT is superior to CT in detecting extranodal disease in the abdomen, especially in the spleen and liver, and BM-based osseous infiltration. PET/CT scan showed higher sensitivity, specificity, and accuracy which led to alteration of disease staging with marked effects on the decision of treatment regimens.

Keywords: Hodgkin lymphoma; non-Hodgkin lymphoma; PET scan; CT scan; Extranodal lesions.

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Background:

A broad category of disorders originating in lymph nodes is represented by lymphomas [1]. Over the course of the last 20 years, a number of World Health Organization (WHO) consensus statements have been published due to the disease's diversity and the challenges associated with diagnosis and categorization [2]. These claims attempted to provide a morphological, immunophenotypic, genomic, and molecular characterisation of the illness [1]. The lack of clarity in these publicly available records also permeates the way the condition is diagnosed and monitored on a daily basis [3].

Lymphoma is a group of diverse cancers caused by clonal lymphocyte growth. It accounts for around 5% of cancers. Overall survival is estimated at 72%. This activity describes the evaluation and management of lymphoma, as well as the role of the interprofessional team in treating patients with this condition. Lymphomas are divided into two types: Hodgkin lymphoma (HL), which accounts for 10% of cases, and non-Hodgkin lymphoma (NHL), which accounts for 90% [3].

Lymphoma, mainly non-Hodgkin's lymphoma (NHL), maybe extranodal in 40% of patients, the term extranodal lymphoma has been used to describe this

form of lymphoid malignancy, in which there is neoplastic proliferation at sites other than the expected native lymph nodes or lymphoid tissue.[4] The observed rising incidence of NHL and Hodgkin disease (HD) in the past two decades has been characterized by a marked increase in the occurrence of extranodal lymphoma.[5] Lymphomas that initially appear to have the bulk of the disease at extranodal sites are described in primary extranodal lymphoma and categorized as Stage I or II. In secondary extranodal lymphoma, there is secondary involvement of the extranodal sites from primary nodal disease, which is categorized as Stage III or IV[6]

Over the past 20 years, the role of Positron Emission Tomography-Computerized Tomography (PET-CT) in the diagnosis and treatment of lymphomas has changed, particularly for aggressive histological types including diffuse large B cell and HL [7, 8]. Numerous studies have demonstrated the sensitivity and specificity of PETCT in terms of prediction, as evidenced by the literature [5]. During the interim evaluation of the response, PETCT is able to reliably anticipate the presence of disease spread inside the bone marrow as well as the efficacy of the selected therapy [9].

The evidence presented in the literature on this topic was examined in this dissertation, together with our own experiences with PET-CT for lymphoma diagnosis and treatment, particularly in patients with extra-nodal illness. We discussed our experience evaluating patients with extra-nodal lymphomas utilizing PET-CT for baseline characterization, interim assessments, and post-therapy evaluations.

The objective of this study was to evaluate the usefulness of PET/CT in the identification and assessment of extranodal lymphoma. We also investigated the experience in evaluating patients with extranodal lymphoma in pediatrics and adults at baseline, intermediate, and post-therapy.

Patients and Methods:

Study design and patients

In this observational study, the results and assessment of PETCT scans performed on lymphoma patients with primary extra-nodal lymphoma or extranodal involvement of advanced nodal lymphomas were investigated.

Study setting

Assiut University Hospital, the Nuclear Medicine Unit.

Selection criteria

Inclusion criteria:

- All Patients with lymphoma were included in the study.
- Adult participants (>18 years).
- Patients underwent pathological confirmation of lymphoma and immunohistochemistry positive for lymphoma.
- Association of extranodal involvement with the nodal disease.

Exclusion criteria:

- Pregnant women.
- Patients with second malignancy.
- Patients with uncontrolled diabetes.
- Non-FDG avid subtypes of lymphoma.

Procedures and measured outcomes

Patients with either primary early-stage extranodal lymphoma or with advanced disease harboring extranodal involvement with be retrieved from the archives and analyzed. Baseline patients' data was retrieved from the archives. These included the age, gender, and disease pathological subtypes. Patients' outcomes whenever available be included in the analysis. The DICOM images of the PET-CT scans were analyzed using Commercially purchased RadiAnt software. The lesion site, characteristics, and avidity were analyzed for each patient and included within the patients' sample.

Patient preparation

The time of PETCT was scheduled to be either four to six weeks from the last session of radiotherapy or recent surgery, two weeks from the last cycle of chemotherapy, or the last dose of granulocytes colony stimulating factor (G-CSF). The patient's blood glucose level was measured before starting the procedures and was ensured to be effectively controlled under 180 mg/dL if being non-diabetic and below 200 mg/dL if being diabetic. Patients were instructed to avoid exercise and cold exposure 24 hours before the study. The patient was instructed to fast for at least 4-6 hours before FDG injection and 3-4 hours in children.

Any woman of reproductive age was screened for possible pregnancy, prior to administering FDG, and Pregnant women were excluded from the study. The lactating mothers were instructed to avoid close contact with the child and delay breastfeeding 4-6 h post radiotracer injection. All patients were informed to avoid exposure to pregnant women and children for at least 4-6 hours after the study.

Radiopharmaceutical: F18-FDG (F18-fluorodeoxyglucose)

The adult patients were injected intravenously with 0.15-0.2 mci/kg F18-FDG while pediatric patients were injected with 0.09-0.1 mci/ kg. Patients are allowed to wait for 45-60 minutes post-injection in a dim light room.

Technique

Standard PET/CT study (skull base to proximal thighs), was done in most cases using a hybrid PETCT scanner. The used PETCT scanner was Siemens © biograph horizon PET/CT with low dose non-diagnostic 16 slice CT scan.

The CT scan was acquired for attenuation correction and image fusion with PET images and anatomical localization, CT images were acquired at 130 KV, in 5mm slice thickness for adults and 1.5 mm slice thickness for pediatrics. The scan window included whole body imaging in craniocaudal direction, followed

by PET imaging in 3D mode which was collected in a caudocranial direction with patient arms up. The whole-body study (skull vertex to toes) was used for patients with cutaneous lymphoma.

Ethical approval

Written informed consent was obtained from all patients participating in the study. The scientific ethics committee approved the study protocol.

Statistical analysis

Procedures of descriptive analysis were applied to the retrieved data. The frequency distribution was obtained and recorded. Correlation was done whenever possible. The commercially available statistical software IBM-SPSS (version 23 for Windows; IBM Inc.) was used for data analysis. An alpha level of 5% was used for all tests to consider the statistical significance. The Mc Nemar test was utilized to compare the numbers of outcomes between the reported imaging modalities.

Results:

A total of 112 patients were included in the analysis were referred to Nuclear Medicine unit from Table (1). The median age of the patients was 40 (2 – 86) years and more than half of the participants (54.5%) were males, The primary pathologies were HL and diffuse large B-cell lymphoma in 44.6% and 22.3% of the included population, while unspecified B-cell lymphomas and other histologies represented 31.2%, and 2%, respectively. B-symptoms were reported in 33.3% of the cohort.

Primary extranodal disease was seen in 37.5% while secondary extranodal pattern (nodal and extranodal disease) was 62.5%. The majority of HL was presented as secondary extranodal (82%). For NHL, primary extranodal accounted for 46.8% Figure (1). The disease stages I, II, III, and IV were seen in 15.3, 16.2, 29.7, and 38.7 percent of the patients, respectively Figure (2).

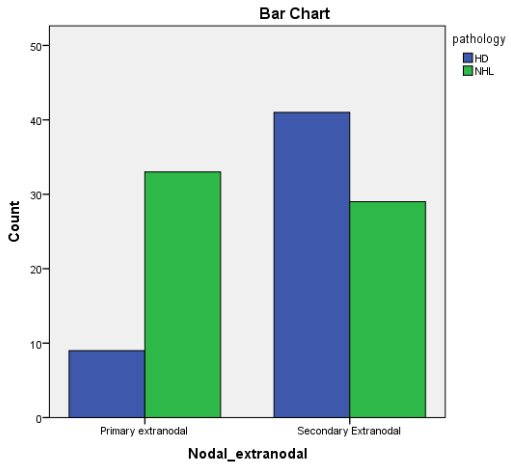


Figure (1): The Proportion of primary and secondary extranodal in HD and NHL.

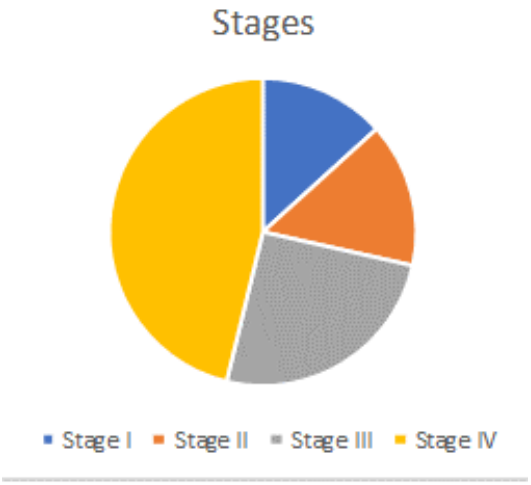


Figure (2): Stages of the disease.

As per scan analysis, the site of the primary lesion was cervical lymph nodes in 82 (52.6%), followed by mediastinal lymph nodes in 19 (12.2%) then para-aortic LNs in 7 (4.5%) and spleen in 7 (4.5%). Another few frequent sites were detected at the bone, axillary LNs, nasopharynx, stomach, and lung. The rarest sites of primary lymphoma lesions were at the orbit, nose, skin, and prostate Table (2).

For patients with initial assessment. the median SUV max for the lesion on initial PETCT was 15.7. range (4 – 41). Of patients having interim assessment, 11.8 % had Deauville score of 1 and 2, while 11.8% had score of 3. Scores 4 and 5 represented 29.4% and 47.1%, respectively. Patients with Deauville 4 and 5. The calculated mean for the SUV max values of the main lesions was 10.0 and 10.3 for HD and NHL, respectively. Also, the mean was 11.1 and 9.7 for primary and secondary extranodal NHL, respectively. At initial staging, PET/CT could detect more nodal and extranodal lesions compared to CT, particularly in the spleen and bone marrow. The McNemar test was found to have a significant difference in the probability of detecting lesions between CT and PET/CT in bone marrow (P = 0.000), lung nodules (P = 0.000), mediastinal (P = 0.01) and para-aortic nodes (P = 0.006) as seen in Table (3).

At the post-therapy evaluation, 17.4% of the population had Deauville 1 and 2, while 4.7% had Deauville 3. Deauville 4 and 5 represented 29.9% and 47.1%, respectively. PET/CT could exclude active lymphatic infiltration from many lesions detected by CT at different sites, lung nodules, cervical, mediastinal, and abdominal LNs, however could detect more bone marrow infiltration, bone, and splenic lesions. McNemar test identified a significant difference in the probability of detecting lesions between CT and PET in BM, lung nodules, and mediastinal and para-aortic nodes Table (3).

In the initial staging, PET/CT detected positive splenic uptake in 27 studies (65.9%), while only one

study showed positive splenic uptake among the interim assessment studies. At post therapy assessment, and follow-up staging, 24 (27.6%) and 7 (43.8%) studies showed positive splenic recurrent lesions. The chi-square test identified a significant difference in the rate of positivity according to the exam setting (P = 0.000) Table (4).

Table (1): Demographic and clinical data of the patient population (n=112).

Parameter	Frequency	Percentage
Age		
Mean	37.49	
Median	34.5	
Range	2-86	
Gender		
Male	61	54.5%
Female	51	45.5%
Pathology of HD (n=50, 44.6%)		
Classical HD	18	36%
Nodular sclerosing	21	42%
Mixed cellularity	11	22%
Pathology of NHL (n=62, 55.4%)		
B cell lymphoma	35	56.5%
DLBCL	25	40.3%
Small	2	3.2%

Table (2): Site of Main Lesions.

Site	Frequency	Percent
Appendix	1	.6
Axillary Node	4	2.5
Bone	5	3.1
Brain	1	.6
Cervical Node	82	50.9
Esophagus	1	.6
Ethmoid	1	.6
Gastric	2	1.2
HFL	1	.6
Iliac Node	2	1.2
Lacrimal Gland	1	.6
Lung Nodule	2	1.2
Mediastinal Node	19	11.8
Nasopharynx	3	1.9
Nose	1	.6
Orbit	1	.6
Oropharynx	1	.6
PA Node	7	4.3
Paravertebral Mass	2	1.2
Parotid	2	1.2
Peritoneum	1	.6
Pharynx	1	.6
Prostate	1	.6
Skin	1	.6
Spine	2	1.2
Spleen	7	4.3
Stomach	1	.6
Thyroid	2	1.2
Tonsil	1	.6
Total	156	96.9

Table (3): CT and PETCT detection rates.

Anatomical site	Detection Rate		McNemar Test, p-value
	PET CT finding	CT Finding	
Initial staging (N=41)			
Head and Neck	32.4%	24.3%	0.50
Lung nodules	17.1%	27.5%	0.219
Spleen	65.9%	41.5%	0.004
BM	37.5%	17.9%	0.008
Liver	10.3%	9.8%	1.0
Bone	22.0%	23.1%	1.0
Cervical Nodes	73.2%	76.9%	1.0
Mediastinal Nodes	75.6%	71.8%	0.5
PA nodes	27.5%	24.4%	1.0
Interim Assessment (N = 17)			
Head and Neck	37.5%	53.3%	0.50
Lung nodules	11.8%	29.4%	0.250
Spleen	5.9%	5.9%	1
BM	5.9%	17.9%	0.5
Liver	0%	11.8%	NA
Bone	50%	52.9%	1.0
Cervical Nodes	41.2%	47.1%	1.0
Mediastinal Nodes	35.3%	47.1%	0.625
PA nodes	17.6%	29.4%	0.5
Posttherapy assessment (N = 87)			
Head and Neck	4.6%	6.9%	1.000
Lung nodules	31%	50%	0.000
Spleen	27.6%	25.6%	1.00
BM	21.8%	5.8%	0.000
Liver	5.7%	10.5%	0.125
Bone	25.3%	22.1%	0.549
Cervical Nodes	47.7%	54.7%	0.180
Mediastinal Nodes	56.8%	69.4%	0.01
PA nodes	48.8%	60.5%	0.006

Table (4): The rate of splenic uptakes within different time settings

	Positive	Negative
initial staging	27 (65.9%)	14 (34.1%)
Interim assessment	1 (5.9%)	16 (94.1%)
Posttherapy assessment	24 (27.6%)	63 (72.4%)
Follow-up staging	7 (43.8%)	9 (56.3%)

30 years old Female patient with Hodgkin disease, nodular sclerosing type. She was presented with a right axillary LN enlargement. PETCT was done for initial staging, and it revealed bone marrow infiltration, SUV 12.2.

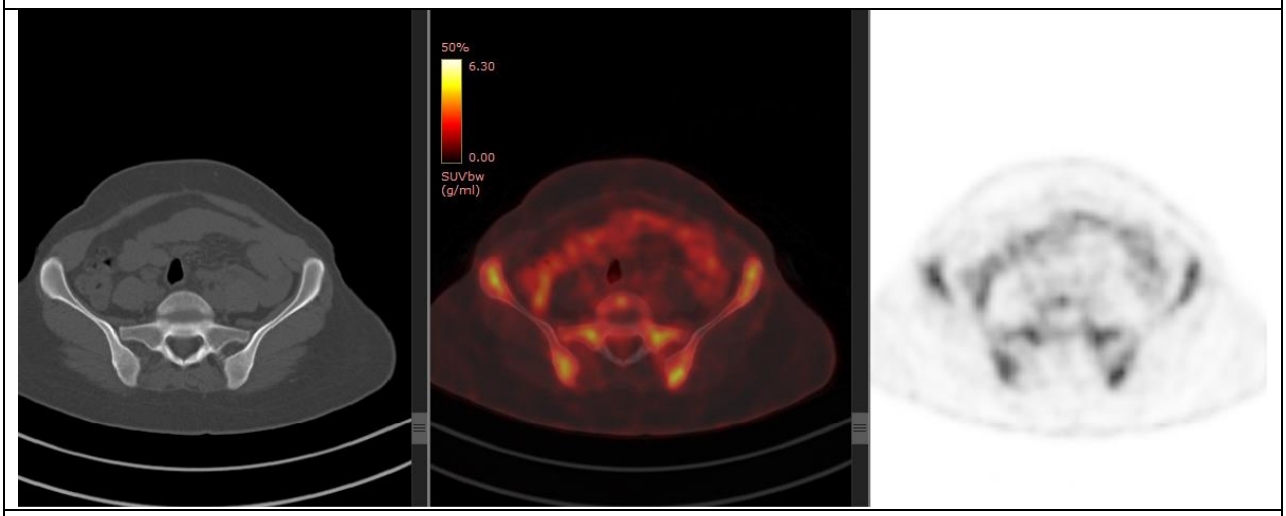
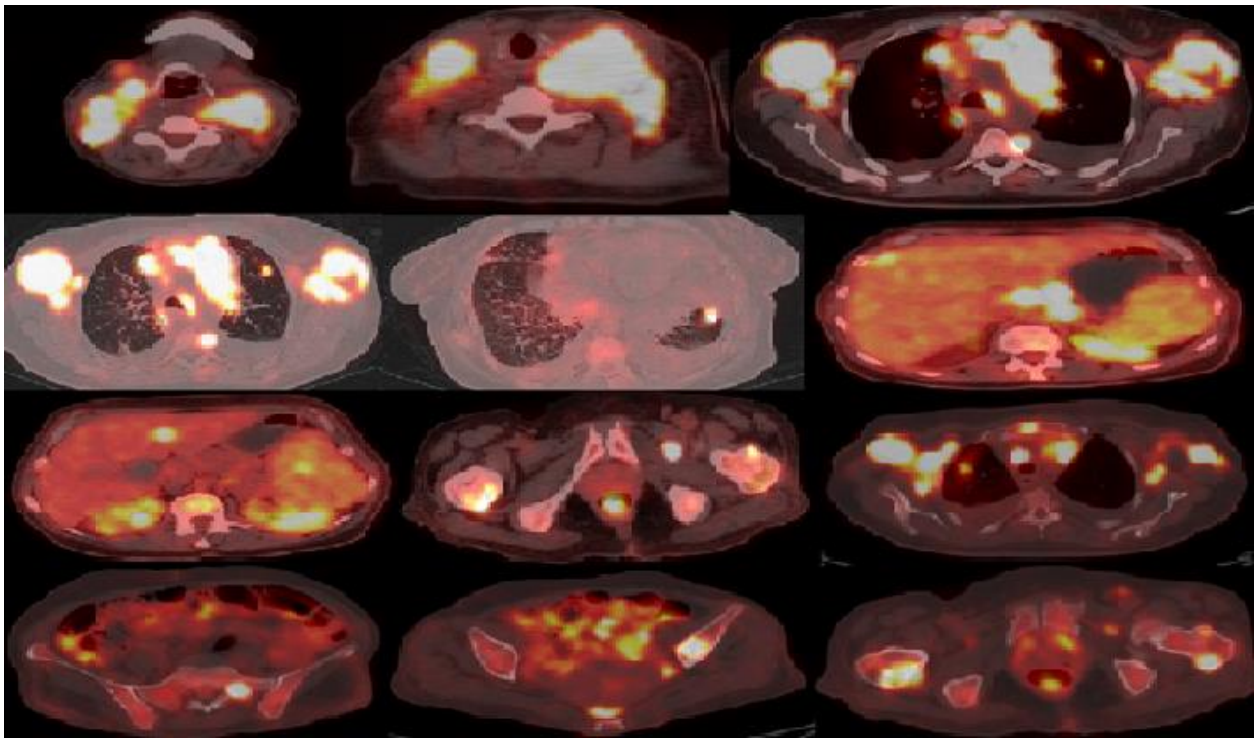
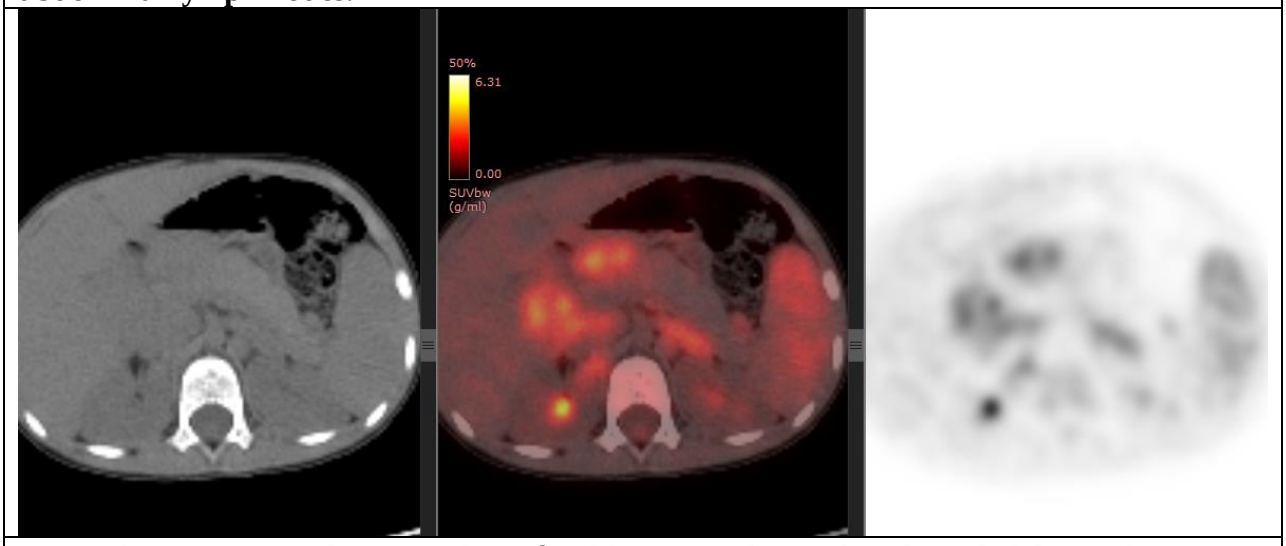


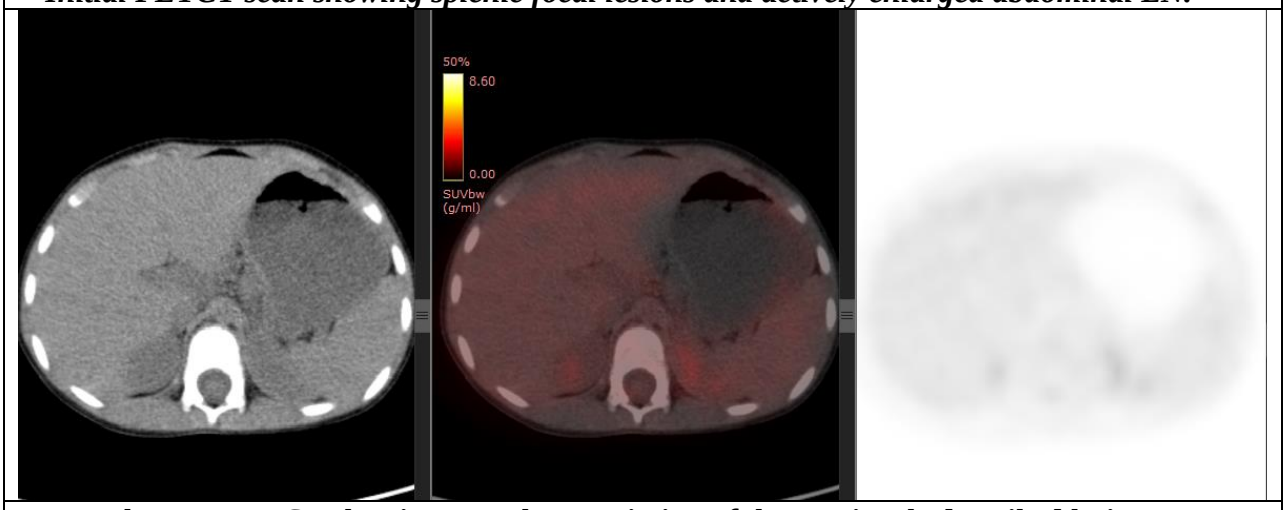
Figure 1 - 30 years old Female with HD - Initial PETCT showed bone marrow infiltration with diffuse uptake



4 years old girl with Hodgkin disease, was presented with cervical lymphadenopathy. PETCT done at initial staging showed multiple FDG uptake splenic focal lesions (SUV 2.6) and multiple abdominal lymph nodes (SUV 4) – reference hepatic SUV 0.9. Patient received chemotherapy and had post-therapy PETCT assessment, which showed almost complete metabolic regression of the previously described spleen focal lesion and the abdominal lymph nodes.

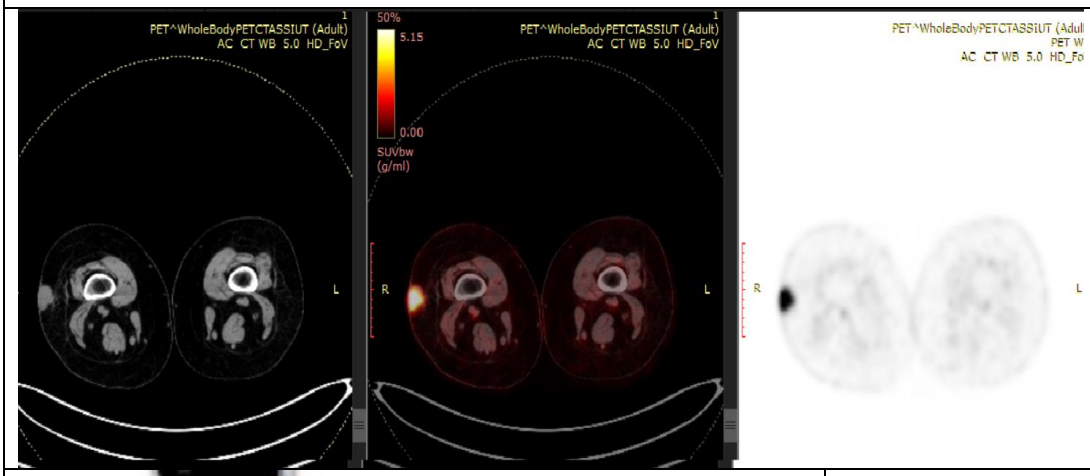


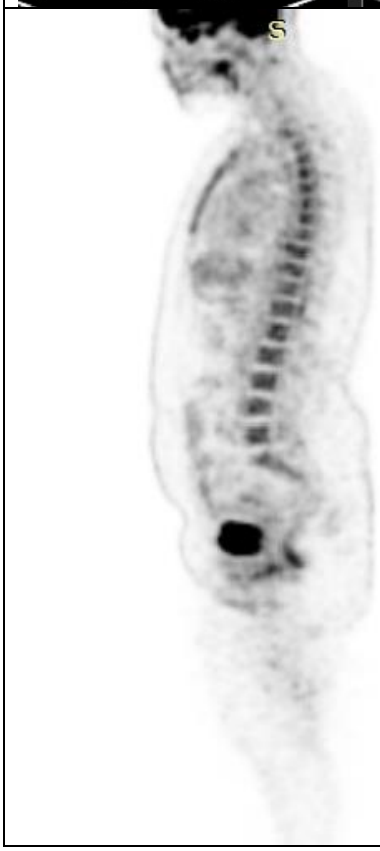
- Initial PETCT scan showing splenic focal lesions and actively enlarged abdominal LN.



- Post-therapy PETCT showing complete remission of the previously described lesions.

42 years old Female patient with non-Hodgkin disease, DLBCL. She was on follow-up for two years. Presented with suspected relapse. PETCT showed diffuse bone marrow uptake and subcutaneous soft tissue lesion (SUV 7.4) - reference hepatic uptake SUV 3.





- PETCT done at time of relapse, showed diffuse bone marrow uptake and subcutaneous active lesion.

Discussion:

The most common clinical feature of lymphoma is enlarged lymph nodes, which may feel hard or rubbery to the touch and are often painless. In some cases, lymphoma can also affect extranodal sites, such as the spleen, liver, bone marrow, or gastrointestinal tract, resulting in abdominal pain, swelling, anemia, or changes to blood cell counts [10].

In our study, we examined 161 scans obtained from 112 patients with extra-nodal lymphoma. 57% of patients were males. This comes in agreement with Ömür et al. whose study showed males are more affected than females. Several Egyptian authors

addressed the question of the prevalence of extra-nodal lymphoma. El-Haddad et al. and Alnouby et al. showed comparable distribution between males and females. Similar to theirs, our study showed that HD and diffuse large B-cell lymphoma represented two-thirds of the patients [11, 12].

In our study, one-third (37%) of patients were presented with primary extranodal disease, which is confined to a single site outside of the lymph nodes. The remaining 62.5% of patients were presented with secondary extranodal disease. However, Othman et al. stated that 10% of patients had primary lymphoma, compared to 90% had secondary extranodal lymphoma with NHL constituting around 80% [13]. The disparity between our study and their study is likely related to selection bias related rather than true differences in disease epidemics.

Our study pointed to the difference in the distribution of primary and secondary extra-nodal presentations between HD and NHL. The majority of HD presentations came in the form of secondary extra-nodal presentations, roughly 82%. However, the distribution of primary and secondary extra-nodal presentations was nearly equal among the NHL patients.

In our study, the highest SUV max value in the HL population (mixed cellularity) was 45 and detected in the pancreaticoduodenal lymph node. However, it was 41 in the NHL population (DLBCL) and was seen in the right tonsillar and oropharyngeal mass. Abdelmohsen et al. stated in their study that the highest SUV max value was 21 and located in gastric lymphoma [14]. Histologically, Othman et al. pointed out that the maximum FDG uptake was seen at NHL (DLBCL) followed by (large B cell lymphoma), while in HD, the maximum uptake was seen in the interfollicular subtype followed by nodular subtype [12]. These results were in agreement with Schroder et al. [15], where the DLBCL, nodular sclerosis types showed the highest FDG avidity.

Furthermore, when comparing CT to PET/CT at initial staging, the latter was able to detect more nodal and extra-nodal lesions, especially in the spleen and bone marrow. By using the McNemar test, we found a significant difference in detection rates between PET/CT and CT for spleen ($P = 0.004$) and bone marrow ($P = 0.008$) lesions. Our study is in line with the previously published data that pointed to the value of PETCT in increasing detection rates of positive spleen and bone marrow infiltration compared to conventional CT scans [16] These results are keeping with the study made by Omur et al. The superiority in detection rate of PETCT compared to CT in bone marrow, spleen, and liver was proved by several authors previously and is in line with our findings [14-16].

Roughly one-third of patients exhibited splenic infiltration. The probability of detecting positive spleen was more seen in the initial staging scans (65.9% versus 34.1%) compared to the other exam setting ($P = 0.000$). Moreover, among patients diagnosed with HD, there was a significantly higher splenic FDG avidity rate compared to those with NHL ($P = 0.000$).

These findings signify and confirm the importance of utilizing PET/CT for initial staging scans compared to other scan settings, especially in HD and detection of splenic disease. As expected, Othman et al. stated that the most frequent extranodal site was the spleen with 30 percent (22 percent focal compared to 8% diffuse) [10]. This was supported by Abdelmohsen et al. who stated that the splenic infiltration was in the range of 25% [17].

PET/CT scanning was shown to be able to accurately rule out active lymphatic infiltration for a number of detected lesions at different sites, including lung nodules, and cervical and mediastinal abdominal lymph nodes. The unique ability of PETCT to characterize lung nodules was also confirmed by previously published data within the literature [18]. This is keeping in agreement with Das et al. [4]; they reported that HD of the lung is rare and usually due to direct extension from a mediastinal or hilar mass. On the other hand, Metser et al. found that lymphoma of the lung is three times more frequent in HD more than NHL. Differentials include granulomatous disease or even second primary malignancy.[20]

In contrast, PET/CT at post-therapy assessment was able to detect more cases of bone marrow infiltration, bone issues, and spleen lesions. The McNemar test was found to have a significant difference in the probability of detecting lesions between CT and PET/CT in bone marrow ($P = 0.000$), lung nodules ($P = 0.000$), mediastinal ($P = 0.01$) and para-aortic nodes ($P = 0.006$).

PET/CT is a highly sensitive and specific imaging technique used in the diagnosis, staging, and monitoring of various cancers, including lymphoma. It can help to identify the extent and location of cancer involvement more precisely than conventional imaging modalities [13, 14]. In lymphoma detection, PET/CT can identify nodal and extranodal lymphomatous sites, that can be either picked up by the CT component, the PET component, or a combination of both resulting in accurate staging for an individual patient with improved disease management, more prompt initiation of treatment, and a better prognosis [15].

Despite the widespread use of PET/CT, there are some limitations of this imaging modality, including non-specific uptake in some inflammatory and infectious conditions, the small size of some primary lesions, and the relatively high cost. Furthermore, PET/CT can miss small neoplastic lesions and can fail to differentiate between viable tumors and post-treatment inflammatory activity, leading to a false-positive interpretation of the scan [16].

PET/CT has been shown to be useful in the diagnosis and staging of extranodal lymphoma. It can detect small foci of disease and is particularly useful for identifying extra-nodal sites of involvement. PET/CT has a higher sensitivity and specificity for detecting extra nodal involvement than other imaging modalities such as CT or MRI [17].

Beyond its clinical utility, PET/CT imaging has also been used in research studies evaluating prognostic factors for extranodal lymphoma. PET/CT parameters,

such as the maximum standardized uptake value (SUV max), have been identified as predictors of survival rates in patients with extranodal lymphoma [18, 19].

PET/CT also plays an important role in the management of extranodal lymphoma, by identifying changes in metabolic activity as a surrogate marker for tumor location and response. For example, PET/CT was more accurate in diagnosis, staging, and response assessment of MALT lymphoma arising from mucosal lining [20, 21].

Conclusions:

Management of lymphoma depends on accurate staging of lymphoma. PET/CT study offers a chance for complete assessment for extranodal lymphomatous infiltration and allows proper staging of lymphoma and enables accurate detection of more extranodal lymphomatous infiltration that helps in up or downstaging the disease. PET/CT is superior to CT in detecting extranodal disease in the abdomen, especially in the spleen and liver, and BM-based osseous infiltration. PET/CT scan showed higher sensitivity, specificity, and accuracy which led to alteration of disease staging with marked effects on the decision of treatment regimens. Early assessment of response to therapy by PET/CT is an important prognostic parameter that is useful for the identification of patients with an increased risk for relapse or progression.

List of abbreviations:

- CT: Computerized Tomography.
- DICOM: digital imaging and communications in medicine
- DLBCL: Diffuse Large B-Cell Lymphoma
- FDG: fluro-deoxy glucose
- HD: Hodgkin disease
- NHL: Non-Hodgkin Lymphoma
- PETCT: Positron Emission Tomography Computerized Tomography.
- SUV: standardized uptake value
- WHO: world Health Organization

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