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ROLE OF PET/CT IN THE INITIAL STAGING AND EVALUATION OF THE THERAPEUTIC RESPONSE IN PATIENTS WITH NON-HODGKIN LYMPHOMA

By

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ABSTRACT

Background: Non-Hodgkin lymphoma (NHL) is a neoplasm of the lymphoid tissues arising from B cell precursors, T cell precursors, mature B cells, and mature T cells. NHL accounts for one of the most common malignant diseases in the general population.

Objective: To assess the importance of positron emission tomography/computed tomography (PET/CT) in the initial staging and evaluation of therapeutic response in patients with NHL.

Patients and methods: Thirty cases, confirmed by histopathology to be NHL, were examined by PET/CT for initial staging and evaluation of therapeutic response.

Results: PET/CT detected 94 total involved sites with sensitivity 100 %, specificity 97.6 %, and accuracy 98.2 % which was larger than sites detected by CT; 80 total involved sites with sensitivity 84.04 %, specificity 91.5%, and accuracy 89.7 %. Regarding to treatment response assessment, PET/CT detected complete regression (60%), partial regression (30 %) stationary course (0%) and progression (10 %) while CT detected complete regression (70%), partial regression (20 %) stationary course (10%) progression (0%).

Conclusion: PET/CT provides more accurate results regarding the staging and treatment response of patients with NHL in comparison with CT declaring a greater sensitivity, specificity, and accuracy.

Keywords: PET/CT; Non-Hodgkin Lymphoma (NHL); Initial staging; therapeutic response.

INTRODUCTION

Lymphomas constitute a varying group of neoplastic processes with lymphocytic origin. These neoplastic processes are clonal B-cell, T-cell or Natural Killer (NK) cells neoplasms in different stages of differentiation. Lymphomas constitute 6% of all tumors and are in charge of 3% of the mortality by neoplastic processes *(Páez et al., 2012)*.

Lymphomas are generally classified into two main categories: NHL and Hodgkin's lymphoma (HL). NHL can generally be classified into two groups: The aggressive and the indolent lymphomas, the latter group having a better prognosis, with a median survival spanning about 10 years *(D'souza et al., 2013)*.

CT used to be the main imaging modality used for staging and follow-up of patients with NHL. CT implies limitations in the detection of pathologic changes in normal-sized lymph nodes and in the evaluation of extra-nodal

involvement as it is based on anatomic changes of size and shape *(Mansour, 2010)*.

In the last decade, metabolic imaging of tumors with 18F-fluoro-2-deoxy-d-glucose (18F-FDG) Positron Emission Tomography (PET) has eased the detection of affected nodal and extra-nodal regions, even when CT has detected no lesions. It also plays a role for more correct staging prior to therapy and post therapy follow up *(Paes et al., 2010)*.

We aimed in this work to assess the significance PET/CT in initial staging and therapeutic response evaluation in patients with NHL.

PATIENTS AND METHODS

In this work, a prospective study was done at Radiology Private Center through the years 2018 and 2021, including patients with NHL who underwent PET/CT scans for staging and therapy monitoring. This study included 30 patients. All of them performed PET/CT scan for initial staging and 10 of them performed additional PET/CT after the end of treatment to evaluate therapeutic response.

Inclusion criteria: Thirty cases (21 males and 9 females) and age from 5 to 72 years were included in this study. All patients underwent physical examination and laboratory analysis for lymphoma. All cases were biopsied for pathological diagnosis of lymphoma.

Exclusion criteria: Any patient with high blood sugar level (> 200mg/ml) at the time of examination. Any patient with absolute contraindication to expose to radiation, e.g. pregnancy.

General electric (GE) Health Care PET/CT scanner was used for scanning and data evaluation.

Patients fasted for at least 6 hours and empty their bladders immediately before scanning. All metallic objects were removed from the patients, and they were given gown to wear. Administration of 18F-FDG was done through An I.V. cannula. Serum glucose was measured before 18F-FDG injection in case of diabetic patients, with maintaining fasting levels at the range of 70–170 ng/dl. Due to accumulation of 18F-FDG in breast milk, breast feeding women were advised to stop breast feeding for approximately 24 hours after the injection.

IV administration of 3-7 MBq/Kg of 18F-FDG was done 45–90 minutes before examination. This period was necessary for the FDG to be distributed and transported into the cells of the patient. The patients were positioned in a comfortable head fixation with arms up.

Scanning started at the level of the skull base and extended caudally to the upper thighs. Scanning parameters included collimation width of 5.0 mm, pitch of 1.5, and gantry rotation time of 0.8 second, and field of view of 50cm.

PET scan was done after the CT scan without moving the patient. For scanning the entire patient, approximately 6 to 7 bed positions are planned in 3D acquisition mode with 3-5 minute acquisition at each bed position.

Axial PET and CT images were first obtained, then reconstructed into coronal and sagittal images to allow image interpretation. The two types of data were then combined together to generate fusion

images. The whole acquisition time for an integrated PET/ CT scan was approximately 25-30 mins. PET image data sets were reconstructed using CT data for attenuation correction and co-registered images were displayed using special software.

A consensus of two experienced observers of nuclear medicine physicians and radiologists analyzed all the PET/CT scans. The PET images and CT images were evaluated for the presence and extent of 18F-FDG in different nodal and extra-nodal sites in the initial studies as well as for residual/recurrent abnormalities during/after therapy.

For measuring the degree of FDG uptake at detected lesions, maximum standardized uptake value (SUVmax) was obtained by applying circular ROI with diameter averaging about 2 cm over the most active part of the lesion.

Lymph nodes were grouped into 5 groups for each patient, including cervical, abdominal, axillary, thoracic and inguinal groups. So, all examined LN groups were 150 per 30 cases. The total number of splenic involvements was 30 per 30 cases whatever the number of its lesions. The total number of bone marrow involvement was 30 per 30 cases whatever the number of its lesions. Other extra-nodal sites were grouped into 6 groups for each patient including head and neck, thorax, GIT, rest of abdomen, osseous, and subcutaneous tissue so the total number of their lesions was180 per 30 cases.

Short-axis diameter more than 10 mm and/or long-axis diameter more than 15 mm were considered as CT criteria for lymph nodal involvement, while presence of any mass lesions or any focal density alterations considered as CT criteria for extra-nodal involvement.

Reevaluation of all lesions detected on CT images was done on fused PET/CT images for estimation of their SUVmax and correlation with FDG uptake by the mediastinal reference background.

Any focus of elevated FDG uptake above mediastinal reference background whether on top of an obvious lesion on CT or not excluding normal areas of physiological uptake.

Staging (according to Lugano classification) of lymphoma, therapy monitoring according to response evaluation criteria in solid tumors (RECIST) and international harmonization project (IHP) criteria were done.

Statistical analysis of data:

The number of lesion, percentages, mean, standard deviation, sensitivity, specificity, and accuracy of each technique were calculated, compared and statistically described using Microsoft Excel 2016.

RESULTS

Large B cell (43.4%) and follicular (20%) were the most represented NHL pathology subtypes in the studied group **(Table 1)**.

Table (1): Histopathological classification of NHL cases in study

Subtypes of NHL	Frequency	Percent
Large B cell	**13**	**43.4**
Follicular	**6**	**20**
Small lymphocytic	**4**	**13.3**
Marginal zone	**4**	**13.3**
Mantel cell lymphoma	**3**	**10**
Total	**30**	**100**

Large B cell lymphoma showed high SUV max in nearly total cases recording in contrast to indolent follicular and marginal zone lymphoma **(Table 2)**.

Table (2): Relation between NHL subtypes and SUV uptake

Subtypes of NHL	Mean SUVmax
Large B cell	**20**
Follicular	**6.5**
Small lymphocytic	**6.5**
Marginal zone	**6**
Mantel cell lymphoma	**11**

CT detected 80 true positive affected sites and 18/98 false positive sites representing a percent of 18.3%. Nodal involvement was truly positive in 65 LN groups with 11 false positive results representing reactive (inflammatory) enlargement and 8 LN groups were false negative. Splenic involvement was truly positive in 6 patients with 3 false positive results. Also, there were 2 false negative results. Bone marrow involvement was truly positive in one patient with 4 false positive result representing degenerative changes with 4 false negative results.

Other extra-nodal involvement was truly positive in 7 extra-nodal organs with 7 false positive results, representing pleural nodule and hepatomegaly, one false negative result. The false negative results in all examined sites were proved to be positive lesions by their increased FDG uptake on PET/CT **(Table 3)**.

Table (3): Descriptive statistics of the number of lesions detected by CT scan

Lesions / Statistics	Lymph nodes	Spleen	Bone marrow	Other extra-nodal involvement
True positive	65	6	1	7
False positive	11	3	4	7
False negative	8	2	4	1
True negative	66	19	21	165

18F-FDG PET/CT detected 94 true positive involved sites and 7/101 false positive sites representing a percent of 6.9%. Nodal involvement was truly positive in 72 LN groups 1 false positive nodal result with no false negative. Splenic involvement was truly positive in 8 patients with 1 false positive result representing splenic abscess correlated with clinical data with no false negative results. Bone marrow involvement was truly positive in 5 patients with 1 false positive result representing hyperemic bone marrow with no false negative results. Other extra nodal involvement was truly positive in 8 extra-nodal organs with 4 false positive results representing chronic tonsillitis and gastritis correlated with clinical data with no false negative results **(Table 4)**.

Table (4): Descriptive statistics of the number of lesions detected by PET/CT scan

Lesions / Statistics	Lymph nodes	Spleen	Bone marrow	Other extra-nodal involvement
True positive	72	8	5	8
False positive	1	1	1	4
False negative	0	0	0	0
True negative	77	21	24	168

The most common involved extra-nodal organ was the spleen (38 %), bone marrow (23.8 %), then thoracic involvement (pleural and intercostal muscle nodules) (9.5%), subcutaneous nodule (9.5 %), GIT (9.5 %), peritoneal involvement (4.7 %) and osseous involvement (4.7 %) **(Figure 1)**.

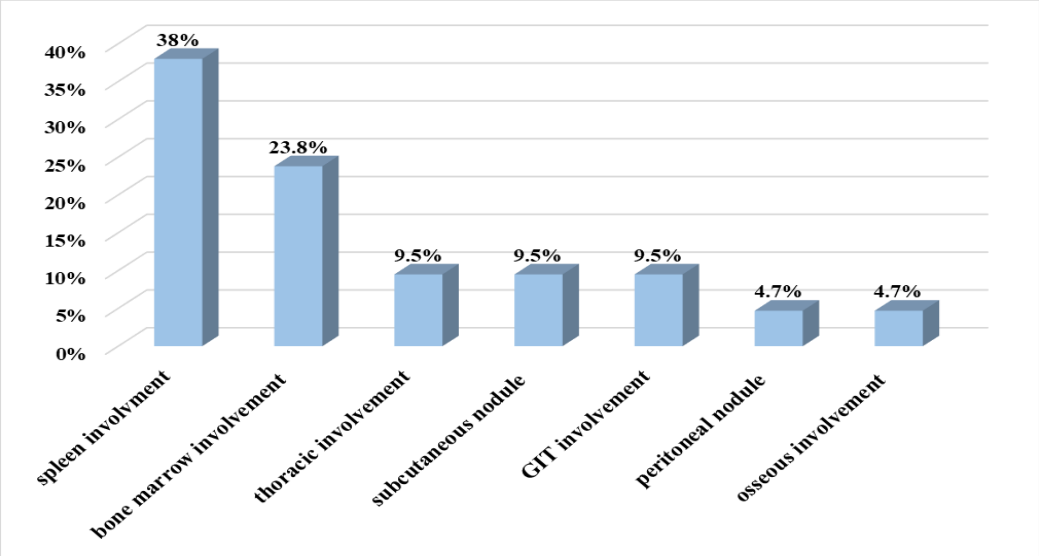


Fig (1): Percentage of involved extra-nodal organs by PET/CT

For total lesions detection, PET/CT showed higher sensitivity 100%, specificity 97.6%, and accuracy 98.2% than CT sensitivity 84.04%, specificity 91.5 %, and accuracy 89.7 % respectively. For lymph nodal involvement: PET/CT sensitivity 100%, specificity 98.7%, and accuracy 99.3% were higher than CT sensitivity 89.04%, specificity 85.7%, and accuracy 95.3% respectively. For splenic involvement: PET/CT sensitivity 100%, specificity 95.4%, and accuracy 96.6% were higher than CT sensitivity 75%, specificity 86.3%, and accuracy 83.3%. For bone marrow involvement: PET/CT sensitivity 100%, specificity 96%, and accuracy 96.6% were higher than CT sensitivity 20%, specificity 84%, and accuracy73.3%. For other extra-nodal organs involvement: PET/CT sensitivity 100%, specificity 97.2%, and accuracy 97.7% were higher than CT sensitivity 87.5%, specificity 95.9%, and accuracy 95.5 % **(Table 5)**.

Table (5): Diagnostic performance of CT and PET/CT scans

Diagnostic performance of CT and PET/CT scans						
parameters	**CT**			**PET/CT**		
	sensitivity	**specificity**	**accuracy**	**sensitivity**	**specificity**	**accuracy**
Total mean	**84.04%**	**91.5 %**	**89.7%**	**100 %**	**97.6 %**	**98.2%**

CT diagnosed 26.6 % of the patients as stage I, 2 of them were diagnosed by PET-CT as stage II and 1 of them was diagnosed by PET-CT as stage IV, so upstaging was 10% patients by PET-CT. CT diagnosed 13.3% of the patients as stage II, 2 of them was diagnosed by PET-CT as stage IV, so upstaging was 6.6% patients by PET-CT. CT diagnosed 16.6% of the patients as stage III, 2 of them were diagnosed by PET-CT as stage IV, so upstaging was 6.6% patients by PET-CT. CT diagnosed 43.3% of the patients as stage IV, 1 of them was diagnosed by PET-CT as stage II, so downstaging was 3.3% of patients by PET-CT **(Table 6)**.

Table (6): Changes in staging according to Lugano classification between CECT and PET/CT

CT Stages / PET/CT Stages	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Total**
Stage I	**6**	**2**	**0**	**1**	**9**
Stage II	**0**	**2**	**0**	**2**	**4**
Stage III	**0**	**0**	**3**	**2**	**5**
Stage IV	**0**	**1**	**0**	**11**	**12**
Total	**6**	**5**	**3**	**16**	**30**

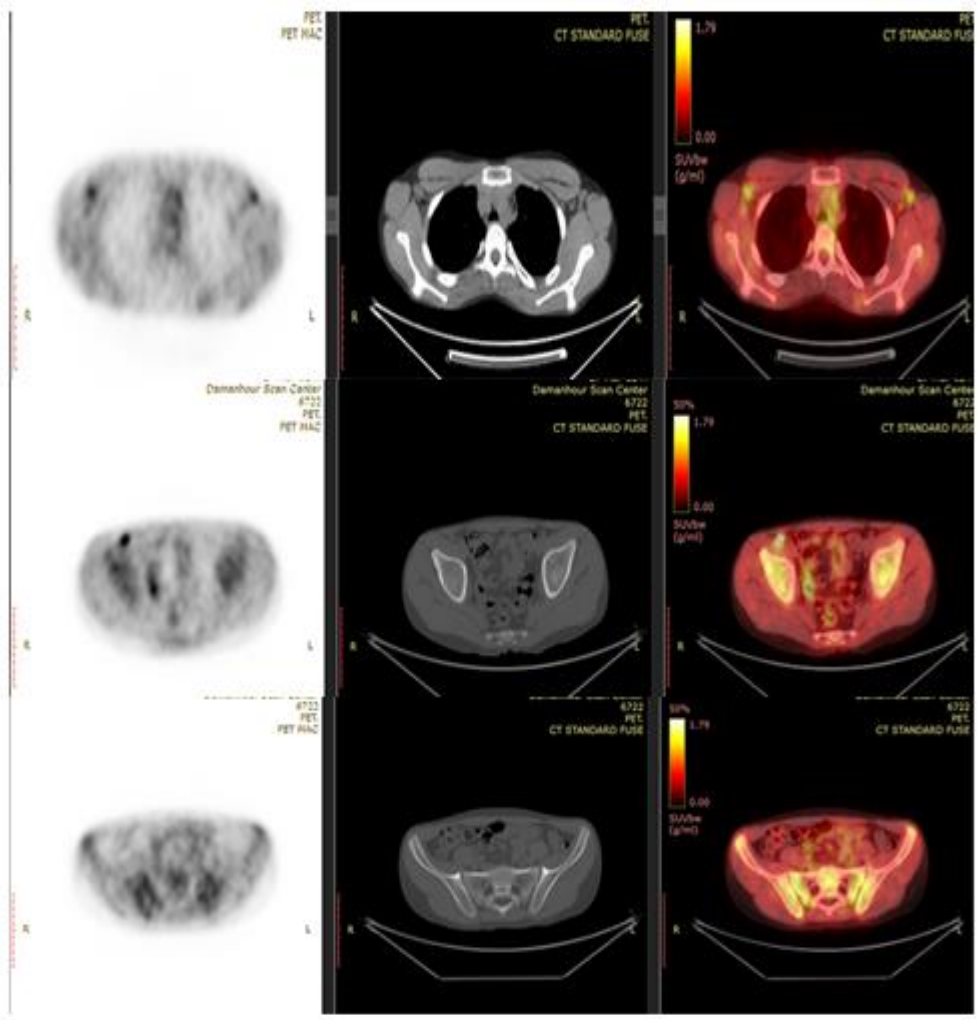
CT detected complete regression (70%), partial regression (20 %) stationary course (10%) progression (0%), while PET/CT detected complete regression (60%), partial regression (30 %) stationary course (0%) and progression (10 %) **(Table 7 and 8)**.

Table (7): CT results in the assessment of treatment response

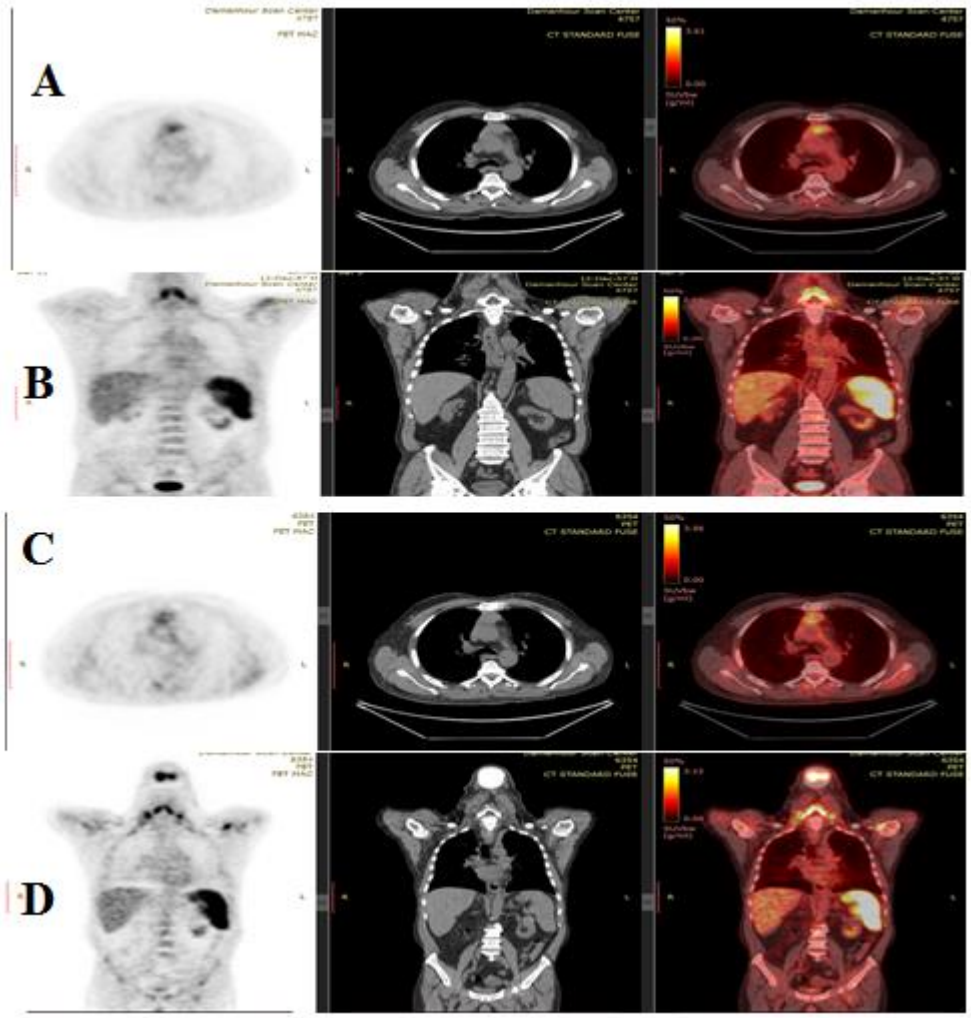
Cases / Response	Frequency	percent
Complete regression	**7**	**70 %**
Partial regression	**2**	**20 %**
Stationary course	**1**	**10%**
Progression	**0**	**0%**
Total	**10**	**100%**

Table (8): PET/CT results in the assessment of treatment response

Cases / Response	Frequency	percent
Complete regression	**6**	**60 %**
Partial regression	**3**	**30 %**
Stationary course	**0**	**0%**
Progression	**1**	**10%**
Total	**10**	**100%**



Case (1): 17 y/o male patient with recently diagnosed NHL, enlarged bilateral axillary LNs with SUVmax up to 3. Rt. external iliac LN. (sub cm) with SUVmax up to3.5. Diffuse heterogeneous bone marrow increased tracer uptake with no concordant CT changes.



Case (2): 61 y/o male patient with NHL. (A and B) baseline PET/CT showing anterior mediastinal mass with SUVmax of 4.6 and mild splenomegaly about 14.5 cm with SUVmax of 5.3. (C and D) post therapy PET/CT. (C): Stationary course regarding the size and SUVmax of the anterior mediastinal mass 4.6 (same as before). (D): mild splenomegaly about 14.5 cm with SUVmax of 6.9 (Vs 5.3 before).

DISCUSSION

CT scan used to be the cornerstone of imaging in lymphoma and was playing a crucial role in staging. Currently, the advances in molecular imaging with 18F-FDG PET/CT scan have facilitated the staging, and response assessment in lymphoma patients *(Johnson et al., 2015)*.

In our study, most cases of large B cell lymphoma showed high SUV value in contrast to indolent follicular and marginal zone lymphoma with mean of SUV max of large B cell equal 20, and mean of SUVmax of follicular lymphoma 6.5 and marginal zone lymphoma equal 6.

This was in agreement with *Wang et al. (2014)* who found that the SUVmax measurements of FDG were significantly different between aggressive and indolent B-cell non-Hodgkin lymphoma.

In our study, PET/CT detected a total number of 94 involved regions with

sensitivity 100 %, specificity 97.6 %, and accuracy 98.2 % which were higher than those diagnosed by CT; 80 involved regions with sensitivity 84.04 %, specificity 91.5%, and accuracy 89.7 %.

Zytoon et al. (2020) showed that PET/CT diagnosed a total number of 545 involved regions with sensitivity 96.6%, specificity 98.8%, and accuracy 99% which were higher than those diagnosed by CT; 439 involved regions with sensitivity 87.5%, specificity 85.7%, and accuracy 88%.

Our study resulted that PET/CT detected 72 true positive nodal group involvements with sensitivity 100%, specificity 98.7%, and accuracy 99.3% which was higher than CT that detected 65 true positive nodal group involvements with sensitivity 89.04%, specificity 85.7 %, and accuracy 95.3 %. Also, there were 8 false negative lymph node groups on CT that decreased to zero groups by PET/CT. This was in agreement with *Ricard et al. (2014)* who stated that the sensitivity of PET/CT 99% was higher than the sensitivity of CT 85% and also detected in their study 32 false negative lymph node groups by CT that was corrected to 3 groups by PET/CT.

In this study, splenic involvement was truly positive in 8 of the patients by PET/CT with sensitivity 100%, specificity 95.4 %, and accuracy 96.6 % which was higher than CT that detected true positive lesions in 6 of the patients with sensitivity 75%, specificity 86.3%, and accuracy 83.3%. There were 2 of the patients with false negative results when assessed by CT alone that was corrected to zero of patients by PET/CT.

In our study, bone marrow involvement was truly positive in 5 of the patients by PET/CT with sensitivity 100 %, specificity of 96%, and accuracy 96.6 % which was higher than CT that detected true positive lesions in one patient with sensitivity 20 %, specificity 84 %, and accuracy 73.3 %. There were 4 of the patients with false negative bone marrow involvement when assessed by CT alone that was corrected to zero patients by PET/CT. PET/CT has become more frequently utilized in detecting lymphomatous bone marrow involvement *(Ujjani et al., 2016)*.

In our study, PET/CT detected 8 true positive other extra-nodal organ involvements with sensitivity 100%, specificity 97.7%, and accuracy 99.5% which was higher than CT that detected 7 true positive extra-nodal organ involvements with sensitivity 87.5%, specificity 95.9 %, and accuracy 95.5%. There was one false negative extra-nodal organ involvements when assessed by CT alone that was corrected to zero extra-nodal organs by PET/CT. In agreement with our results. *Ricard et al. (2014)* stated that PET/CT sensitivity in detection of extra-nodal lymphomatous involvement 88% was higher than that of CT alone 78%, and that 9 false negative extra-nodal results by CT were corrected to 5 by PET/CT

Differences in staging by PET/CT and CT were found in our study. Discordant staging by both modalities was found in 26.6% of the patients. Lymphoma was upstaged by PET/CT in 23.3% of patients and down-staged in 3.3%. *Othman et al. (2019)* mentioned that 10% of the patients

were upstaged while 5% were down-staged after PET/CT.

In our work, out of the 10 cases, PET/CT and CT were concurrent in results in (80%), and discordant in (20%). CT detected complete regression in (70%), partial regression in (20 %), stationary course in (10%), and no progression, while PET/ CT detected complete regression in (60%), partial regression in (30%), no stationary course, and progression in (10%). *Riad et al. (2010)* assessed early response to chemotherapy in their study; CT and PET/CT were discordant in 33.3%: 29.4% of them were false positive in CT, while in PET/CT showed total remission. In the remaining two cases, one was true positive in PET/CT where it showed active nodal disease in a normal size lymph node in CT which was pathologically proven later as lymphoma, while in the other case, the PET/CT was false positive in detecting diffuse hypermetabolism in the bowel which was proven by biopsy to be an inflammatory process not lymphomatous infiltration.

CONCLUSION

PET/CT has a higher sensitivity and accuracy in patients with NHL. It provided significantly more accurate information compared to CT for the staging and treatment response assessment.

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دور التصوير بالإنبعاث البوزيتروني المدمج مع الأشعة المقطعية في التخطيط الأولي وتقييم الإستجابة للعلاج لدي مرضي سرطان الغدد الليمفاوية الغير هودجكن

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خلفيـــة البحـــث: ســـرطان الغـــدد الليمفاويـــة الغيرهـــودجكين هـــو ورم فـــي الأنســـجة اللمفاويـــة ينشـــأ مـــن ســـلائف الخلايـــا البائيـــة، وســـلائف الخلايـــا التائيـــة، والخلايـــا البائيـــة الناضـــجة، والخلايـــا التائيـــة الناضـــجة. وهـــو يمثـــل أحد أكثر الأمراض الخبيثة شيوعًا بين عامة السكان.

الهـــدف مـــن البحـــث: تقيـــيم أهميـــة التصـــوير بالإنبعـــاث البـــوزيتروني المـــدمج مـــع الأشـــعة المقطعيـــة فـــى التـــدريج الأولـــي، وتقيـــيم الاســـتجابة العلاجيـــة للمرضى المصابين بسرطان الغدد الليمفاوية الغير هودجكين.

المرضـــى وطـــرق البحـــث: تـــم فحـــص ثلاثـــين حالـــة مؤكـــدة مـــن قبـــل التشـــريح المرضـــي كســـرطان الغـــدد الليمفاويـــة الغيرهـــودجكين باســـتخدام التصـــوير بالإنبعـــاث البـــوزيتروني المـــدمج مـــع الأشـــعة المقطعيـــة لتحديـــد المرحلـــة الأولية وتقييم الاستجابة العلاجية.

نتـــائج البحـــث: تـــم الكشـــف بواســـطة التصـــوير بالإنبعـــاث البـــوزيتروني المـــدمج مـــع الأشـــعة المقطعيـــة عـــن 94 موقعًـــا متورطًـــا إجمـــالاً بحساســـية 100٪، ونوعيـــة 97.6٪، ودقـــة 98.2٪، وهـــي أكبـــر مـــن المواقـــع التـــي تـــم الكشـــف عنهـــا بواســـطة التصـــوير المقطعـــي. إجمـــالي 80 موقعًـــا متورطًـــا بحساســـية 84.04٪ ونوعيـــة 91.5٪ ودقـــة 89.7٪. وقـــد تـــم الكشـــف بواســـطة التصـــوير بالإنبعـــاث البـــوزيتروني المـــدمج مـــع الأشـــعة المقطعيـــة

عن الانحدار الكامل (60٪)، الانحدار الجزئي (30٪)، المقرر الثابت (0٪)،والتقدم (10٪)، بينما كشف التصوير المقطعي المحوسب عن انحدار كامل (70٪)، انحدار جزئي (20٪)، مسار ثابت (10%)، و تقدم (0%).

الإستنتاج: يقدم التصوير بالإنبعاث البوزيتروني المدمج مع الأشعة المقطعية نتائج أكثر دقة فيما يتعلق بالتدريج واستجابة العلاج للمرضى المصابين بسرطان الغدد الليمفاوية الغيرهودجكين بالمقارنة مع التصوير المقطعي.

الكلمات الدالة: التصوير بالإنبعاث البوزيتروني المدمج مع الأشعة المقطعية، سرطان الغدد الليمفاوية الغيرهودجكين، التدريج الأولي، إستجابة علاجية.