Value of (^{18}F)-FDG PET/CT Scan as a New Imaging in Tumour Staging and Therapy Monitoring of Lymphoma

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Abstract: Background: The purpose of this study was to highlight the advantages and pitfalls of combined (^{18}F)-FDG PET/CT scanning in diagnosis and follow up of lymphoma. **Patients and Methods:** (52) patients who clinically diagnosed as lymphoma underwent (^{18}F) FDG PET/CT scan in the radiology department between the year (2011-2012) for staging and therapy assessment. **Results:** Positron emission tomography (PET) with glucose analog fluorine 18 (fluorodexoglucose) (^{18}F FDG) is increasingly recognized as a powerful evaluation imaging modality in lymphoma. It enables detection of increased glucose metabolic rate that is characteristic of most malignant cells. Useful for initial diagnosis, staging, recurrence and evaluation of therapeutic response. **Conclusion:** Combined (^{18}F) FDG PET/CT proved more accurate diagnostic modility than CT because of its ability to differentiate viable tumour from post therapy necrosis or fibrosis. Also depict residual mass in patients without clinical or biochemical evidence of the disease. Therefore it is a noninvasive modality of choice for lymphoma classification.
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1. Introduction

Since the early (2000s), assessment of lymphoma has been based on clinical examination, CT and bone marrow biopsy (BMB) ***(Zelenetz et al., 2010)***.CT has been the main imaging technique used for the staging and follow up of lymphoma. The fact that CT assessment of disease is based on anatomic criteria of size and shape and abnormal contrast enhancement implies limitations in the depiction of pathologic changes in normal sized lymph nodes and in the assessment of extra-nodal disease ***(Strobel et al., 2007).***

The advantages of ^{18}F-FDG PET/CT for the staging and restaging of both NHL and Hodgkin disease are mostly attributed to the detection of the ^{18}F-FDG-avid, normal-sized lymph nodes (usually <1 cm), and of extra-nodal sites that were previously missed at CT (most commonly the liver, spleen, cortical bone, bone marrow and skin). In a few cases, para-spinal and pulmonary lesions that were interpreted as benign at CT are seen to be malignant at PET/CT. ***(Paes et al., 2010).***

Residual, even bulky masses after therapy completion are frequent in both Hodgkin and NHL correlate poorly with survival. Masses often do not regress completely after adequate treatment because of fibrosis and necrotic debris. It has been demonstrated that adding PET to post therapy CT is especially useful in identifying which of these patients have achieved satisfactory functional remissionc ***(Juweid, 2011).***

PET/CT adds a new dimension to response and risk assessment in lymphoma. There is potential not only to improve the outcomes of suboptimally responding patients but also to spare low-risk patients from overly aggressive treatment. Thus, more precise tailoring of the treatment.

Aim of Work

To analyze the most important applications of FDG-PET (FDG-PET/CT) in lymphoma, emphasizing the strengths and pitfalls of this imaging, particularly in response assessment and therapy monitoring.

Also highlighting the advantages obtained by using combined PET/CT in-line system than the advantage gained by using each modality alone.

Interpretation of PET/CT Scans

Assessment of radiotracer uptake:

The standardized uptake value (SUV) of a lesion is calculated to determine if the lesion is more likely to be benign or malignant. The SUV is dependent on many variables, including body mass and the region of interest. It is higher in obese patients and with smaller regions of interest ***(Reske & Kotzerke, 2001).***

Standardized Uptake Value

The SUV is a unit-less ratio that can be understood as the concentration of ^{18}F-FDG within a lesion divided by the concentration of radiotracer distributed throughout the body. Mathematically, it can be expressed as follows:

SUV=C(T) (dose injected/body weight)

Where (C) is the tissue concentration of ^{18}F-FDG at time (T) ***(Workman & Coleman. 2006)***.

SUV measurement is directly proportional to metabolic activity. SUV is used most frequently in the evaluation of a solitary pulmonary nodule, where an SUV of (2.5) or greater within that nodule is considered suspicious for malignancy, and an SUV less than (2.5) favors a benign. Another major use of SUV is in the follow up since it provides a semi-quantitative index for determining the effect of therapy ***(Workman & Coleman, 2006).***

A) Sites of normal ^{18}F-FDG uptake:

Brain Since it is exclusively dependent on glucose metabolism ^{18}F-FDG accumulation is most intense in the cerebral cortex, basal ganglia, thalamus and cerebellum ***(Kostakoglu et al., 2004). Myocardial up-take*** is variable in patients who have fasted for 4 -18 hours. ^{18}F-FDG is excreted by the ***kidneys***, and intense activity is seen in the *ureters* and *bladder* ***(Pannu et al., 2004).*** Less radiotracer activity is present in the ***liver***, ***spleen***, ***bone marrow***, and ***renal cortex***. One hour after radiotracer injection, blood pool activity results in moderate background activity in the ***mediastinum***, whereas ***lung*** activity is low Significant ***skeletal muscles uptake*** is observed with exercise. ***Brown fat*** is an important cause of altered ^{18}F-FDG bio-distribution involved in thermoregulation prior to the point of shivering. It is often found in the neck, along the spine, and occasionally in the abdomen. Patients that are cold may show spotty uptake in the neck and along the spine due to the brown fat. ^{18}F-FDG uptake is typically bilateral and symmetric. Uptake more common in children than in adults and is most common during the winter. ***(Parysow et al., 2007) Lymphatic tissues*** and ***salivary glands*** uptake may also be seen as a normal variant. Normal ***stomach***, ***small intestine***, and ***colon*** may demonstrate increased ^{18}F-FDG uptake due to a combination of factors, including smooth muscle contraction and metabolically active mucosa. ***(Kostakoglu et al., 2004)***

B) Sites of Benign Pathologic ^{18}F-FDG Uptake:-

Healing Bone: healing bone is associated with elevated ^{18}F-FDG uptake. ***(Meyer et al., 1994).*** **Lymph nodes**: ^{18}F-FDG uptake in lymph nodes is not specific for a malignant neoplasm. Active granuloma such as tuberculosis and sarcoidosis cause high ^{18}F-FDG uptake ***(Strauss, 1996).*** **Joints**: increase uptake of ^{18}F-FDG around joints is particularly seen with periarticular inflammation ***(Jadvar and Parker, 2005).***

2. Patients and Methods

This is a retrospective study carried out in cancer Institute Radiology department between (2011-2012) for patients who have done PET/CT scans for staging and therapy assessment in lymphoma. Patients included in this study were pathologically proven HD or NHL. All exams were done on the PET/CT scanner (General Electric) 64 machine,

We classified the patients into 5 groups;

Group I*: included* **17** patients with pathologically proven HD or NHL, came for initial staging by PET/CT exams.

Group II: out from the above **17** patients, only **7** patients continued interim, end of treatment and follow up exams, and these **7** patients constituted the population of group II. They are included in the first group (initial staging) as a part from the patients characteristics but were analyzed separately.

Group III: included only 13 patients whom started treatment and came to us for ***interim PET/CT*** for response after mid treatment. No previous data were available with them.

Group IV: included 11 patients that were staged and were primarily seen for ***end of treatment.***

Group V: included **7** patients that ended treatment months ago and came to detect disease relapse.

Group VI: included 4 patients with lesions of indeterminate initial histopathologic results and came for ***further characterization of the lesions*** lymphoma was diagnosed by PET/CT and proved later histologically an active lesions.

Patient Preparation;

All patients were asked to fast six hours prior to scan. All metallic items were removed from the patient. An I.V. cannula was inserted for administration of ^{18}F-FDG. The patients were instructed to avoid any activity prior to the examination and following injection of the radioisotope to avoid physiologic uptake. In case of diabetic patients; serum glucose was routinely measured prior to ^{18}F-FDG injection, and fasting levels were 70–180 mg/dl. Diabetic patients should not have regular insulin administered subcutaneously within four hours of having FDG administered. Our strategies for decreasing brown fat were warm environment and high-fat with low-carbohydrate diet before the examination.

Dosage Administration:

We administered one liter of negative oral contrast agent (5% mannitol) approximately one hour before and of 10-20 mCi 370 MBq; approximate dose to patient (3-5MBq/Kg) ^{18}F-FDG 45–90 minutes before examination**.** This period is referred to uptake phase and is necessary for FDG adequately bio-distributed and transported into the patient's cells. To minimize physiologic uptake, the patients should be relaxed with head fixation and arms up.

CT Technique

Non enhanced CT was performed first followed by contrast enhanced CT following injection of (125 mL) of a low-osmolarity iodinated contrast medium. The whole body PET/CT study (neck, chest, abdomen,

and pelvis), scanning began at the skull base and extended to the level of the mid-thighs. The total length of CT coverage was an integral number of bed positions scanned during acquisition of PET data. The study was performed with the patient breathing quietly. Scanning parameters used a collimator width of (5.0 mm), pitch of (1.5), gantry rotation time of (0.8 second), with field of view of (50cm). The data are retrospectively reconstructed at one mm intervals. The whole body study took (20-30minutes).Hundreds of axial PET and CT images were first reconstructed, then reformatted into coronal and sagittal images to facilitate image interpretation using special software.

Timing of exam:

According to **Paes *et al.* (2010),** we performed PET at least (4–6) weeks after surgery or chemotherapy and (8–12) weeks after external beam radiation therapy. These waiting times represent a trade-off between a reliable clinical response and the chances of false-positive and false-negative findings.

PET/CT film Interpretation

All PET/CT examinations were analyzed by at least two experienced observers of nuclear medicine physician and radiologist. The PET images and CT scans were evaluated for the presence and extent of ^{18}F-FDG-positive lymphoma in different lymph nodes groups. Presence of extra-nodal disease and ^{18}F-FDG-negative structural residual soft-tissue abnormalities during/after therapy. Patients were staged according to the ***Ann Arbor classification***, abnormal ^{18}F-FDG uptake was defined as radiotracer accumulation outside sites of usual physiologic uptake and of greater intensity than background activity. Lymph node chains were grouped into supra and infra diaphragmatic regions. The number of sites affected was assessed as either single or multiple. Extra-nodal sites were evaluated: lung, liver, spleen, gastrointestinal, bone, bone marrow and others.

According to the IHP definitions visual assessment alone was adequate for interpreting PET findings as positive or negative. Residual masses of (2 cm) or more in greatest transverse diameter (GTD) with ^{18}F-FDG activity visually exceeding that of mediastinal blood pool structures are considered PET positive, whereas residual masses (1.1 to 1.9 cm) are considered PET positive only if their activity exceeds surrounding background activity. A smaller residual mass or a normal-sized lymph node e.g. (<1×1 cm) should be considered positive for disease if its activity is higher than that of the surrounding background. Diffuse splenic involvement was diagnosed when the splenic activity exceeded that of the liver. Hepatic or splenic lesions(<1.5 cm) on CT should be considered as positive for lymphoma if their uptake is higher than or equal to that of the liver or spleen, and negative if their uptake is lower than them. Lung nodules (≥ 1.5 cm) in patients should be considered as positive for lymphoma if FDG uptake is greater than the mediastinal blood pool. It cannot be excluded in lung nodules (>1.5 cm). If there was multifocal increase in FDG uptake in bone marrow, the patient was considered as PET positive. The diffuse uptake pattern of bone marrow hyperplasia after chemotherapy, can mimic or mask bone marrow involvement; therefore appropriate history was critical. A delay of (3–4) weeks after completion of therapy permits the physiologic marrow activity to abate.

Statistical analysis:

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases), Exact test was used when the expected frequency is less than(5. *P*) values less than 0.05 was considered statistically significant.

3. Results: Results for Group I

From the (**17)** patients in the staging group, there are (**11)** patients, whom PET/CT depicted avid sub-centimetric lymph nodes, (**6)** (**35.3 %**) of them were not detected at contrast-enhanced CT led to their disease upstage. About (**6)** patients of this group had evidence of nodal and extra nodal disease involvement, and (**2)** patients with only depicted extra-nodal disease. **Table (1).**

Table 1: Showing percent & number of patients with lymph nodes and extra nodal involvement in group I

Disease involvement	Number of patients	Percent
Nodal only	9	52.9%
Nodal / Extra-nodal	8	47.1%

Table 2: Showing the distribution of lymph nodes groups involvement in group I in relation to diaphragm.

Distribution of disease	Number of patients	Percent
Supra	8	47.1 %
Infra	4	23.5 %
Supra and infra	5	29.4 %
Total	17	100 %

Table 3: Showing different sites of the extra-nodal disease in group I.

Sites of extra-nodal disease	Number of patients	percent
Osseous / Bone marrow	2	11.7 %
Hepatic	1	5.8 %
GIT	2	11.7 %
Pulmonary nodules	2	11.7 %
Pericardium	1	5.8 %
others	3	17.6 %

Table 4: Showing the initial Staging of the patients in group I.

Staging	Number of patients	Percent
I	0	0%
I-E	0	0%
II	5	29.4%
II-E	1	5.9%
III	2	11.7%
III-S	2	11.7%
I-S	0	0%
IV	7	41.2%
IV-S	0	0%
Total	17	100.0%

Results for Group II

Table 5: Showing percent and number of patients with affected LNs in group II

Disease Involvement	Number of patients	Percent
Lymph Node	5	71.4%
Extra-Nodal	2	28.6%
Total	7	100.0%

Table 6: Showing disease distribution in group II..

Distribution	Number of patients	Percent
Supra	4	57.1%
Infra	1	14.3%
Supra and infra	2	28.57%

Table 7: Showing the different sites and percent of the extra-nodal disease in group II.

Sites of extra-nodal disease	Number of patients	percent
Osseous	1	14.3%
GIT	1	14.3%
Soft tissue	1	14.3%

Table 8: Showing different stages of the patients in group II

Staging	Number of patients	Percent
I	0	0%
I-E	0	0%
II	3	42.9%
II-E	0	0%
III	1	14.3%
III-S	1	14.3%
I-S	0	0%
IV	2	28.5%
IV-S	0	0%
Total	7	100.0%

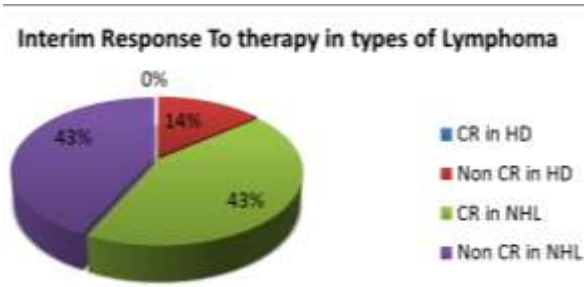

Fig. 1: Showing relation between pathology and response after interim exams in group II (Pie Chart).

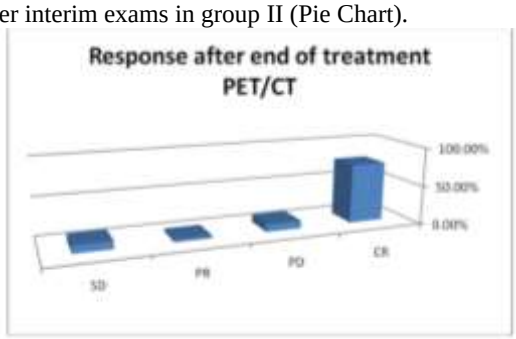

Fig. 2; Showing the response after end of treatment PET/CT exams in group II

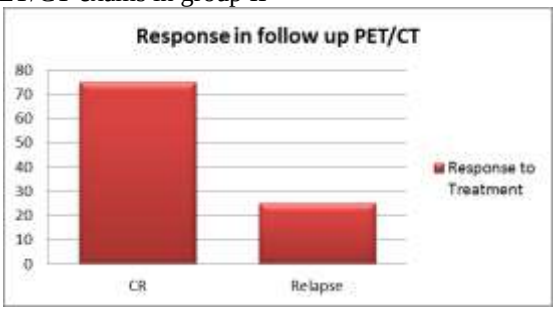

Fig. 3: Showing response after follow up PET/CT in group II.

Results for group III

Table 9: showing the percent and number of patients with active tumor biology in interim PET/CT in group III.

	Number of patients	Percent
Negative	2	15.3%
positive	11	84.7%
Total	13	100.0%

Table 10: Showing the distribution of disease in group III.

Distribution	Number of patients	Percent
Supra	4	30.8%
Infra	1	7.7%
Supra & infra	6	46.1%
Negative patients	2	15.4%
Total	13	100.0%

Table 11: Showing the number of lymph nodes groups affected in group III

Number of lymph nodes groups affected	Number of patients	Percent
No lymph node affection	2	15.4%
Multiple	10	76.9%
Single	1	7.7%
Total	13	100.0%

Table 12: showing number and percent of patients with and without extra-nodal disease in group III

Extra nodal disease		Number of patients	Percent
	Negative	8	61.5%
	Positive	5	38.5%
	Total	13	100.0%

Table 13: Showing the different sites of extra-nodal disease in group III.

Sites of extra-nodal disease	Number of patients	percent
Osseous	3	30%
Hepatic	2	20%
GIT	1	10%
Pulmonary	2	20%
Other	2	20%

Results for group IV

Table 14: Showing the number of patients with active disease in group IV. Fig. 6 (c,d).

Active disease		Number of patients	Percent
	Negative	6	54.5%
	Positive	5	45.5%
	Total	11	100.0%

Table 15: Showing the distribution of disease in group IV.

Sites of lymph nodes groups affected	Number of patients	Percent
supra	4	80.0%
infra	0	0.0%
Both	1	20.0%
Total	5	100.0%

Results for group V

Table 16: Showing the number of patients with affected lymph nodes in group V.

Lymph node affection		Number of patients	Percent
	Negative	3	42.8%
	Positive	4	57.2%
	Total	7	100.0%

Table 17: Showing the distribution of lymph nodes groups affected in group V.

Distribution	Number of patients	Percent
Infra	1	25.0%
Supra	1	25.0%
Both	2	50.0%

Table 18: Showing the number of patients with extra nodal involvement in group V.

Extra nodal disease		Number of patients	Percent
	Negative	6	85.7%
	Positive	1	14.3%
	Total	7	100.0%

Table 19: Showing the response assessment after follow up PET/CT exams in group V.

Response		Number of patients	Percent
	CR	3	42.9%
	Relapse	4	57.1%
	Total	7	100.0%

Results for group VI

Table 20: Showing the distribution of lymph nodes groups affected in group VI.

Distribution	Number of patients	Percent
Infra	0	0.0%
Supra	1	25.0%
Supra & infra	3	75.0%

Table 21: Showing the number of patients with extra nodal involvement in group VI.

Extra nodal disease		Number of patients	Percent
	Negative	3	75.0%
	Positive	1	25.0%
	Total	4	100.0%

Case No. 1: (43) years old female complaining of generalized pain, and multiple palpable lymph nodes. Previous investigations were unremarkable, PET/CT was requested to ***assess nature of lymphadenopathy.***

Metabolically active supra and infra-diaphragmatic lymph-nodes, the largest at the right inguinal region with maximum SUV = 7. No extra nodal metabolically active FDG avid lesions could be noted.The possibility of lymphoma. Nodal excisional biopsy from the inguinal lymph nodes was recommended. The biopsy revealed large cell NHL and the patient was staged according to the primary PET/CT as: Stage III Fig. 1 (a,b,c,d).

The patient underwent radio and chemotherapy, and came back for ***interim assessment*** and revealed single left axillary lymph node with avid-FDG uptake. Findings consistent with: Partial Response Fig. 2(c,d).

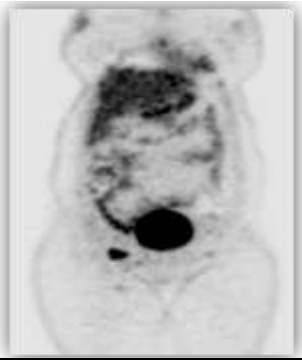

Fig. 1a: Coronal MIP PET image

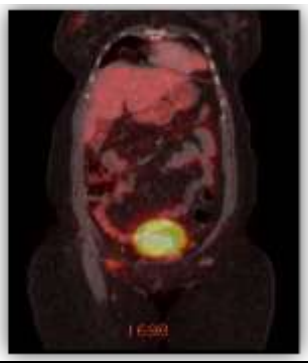

Fig. 1b: Coronal PET/ CT fused image

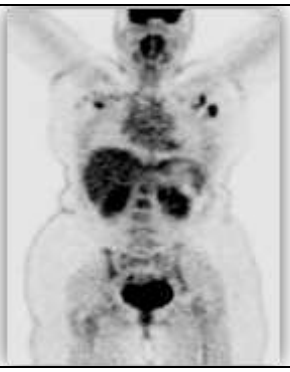

Fig. 1c: Coronal MIP PET image

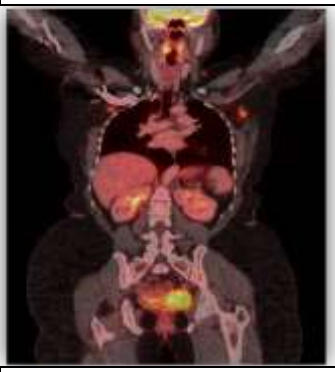

Fig. 1d: Coronal PET/ CT fused image

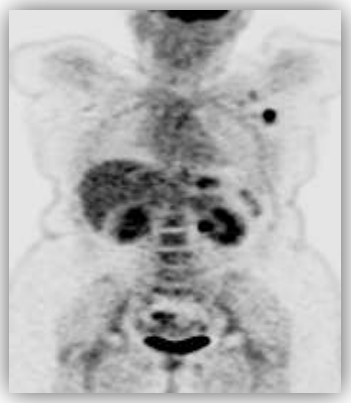

Fig. 2a: Coronal MIP PET image.

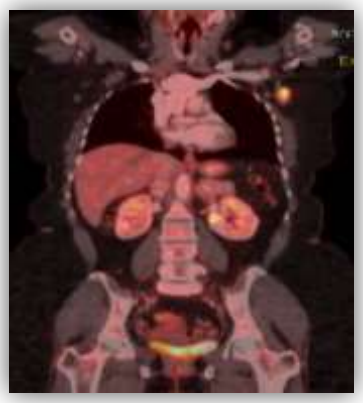

Fig. 2b: Coronal PET/CT fused image.

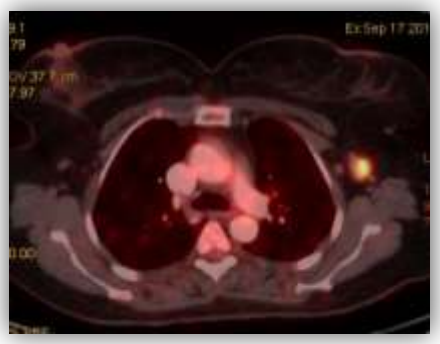

Fig. 2c: Axial PET/CT fused image.

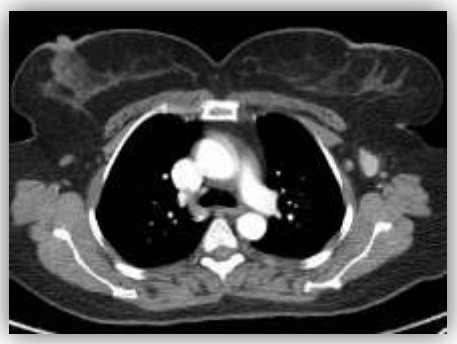

Fig. 2d: axial CT image.

Case No. (2): (47) years old female patient, coming for ***primary staging*** of pathologically proven NHL.

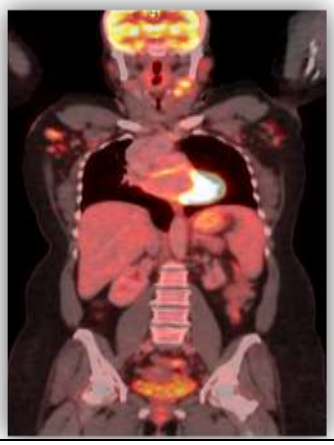

Fig. 3a: Coronal PET/CT fused image.

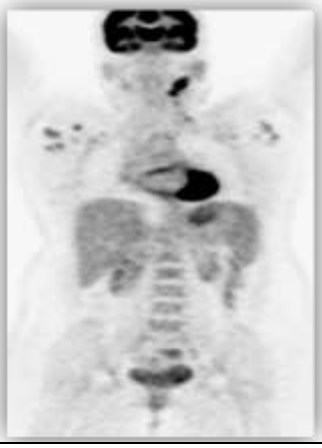

Fig. 3b: Coronal MIP PET image.

The whole body PET and PET/CT images (Fig.3a&b) show multiple metabolically active supra-diaphragmatic lymph nodes group noted at bilateral axillary and cervical lymph nodes, showing SUV max reaching up to 10.

Case No. 3, (59) years old male patient, coming for ***initial staging*** of pathologically proven NHL

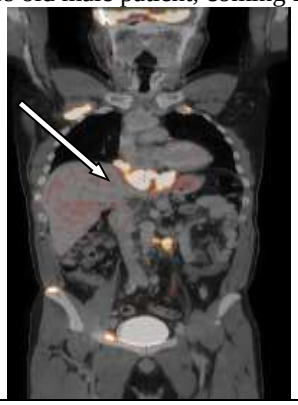

Fig. 4a: whole body coronal PET/CT fused image.

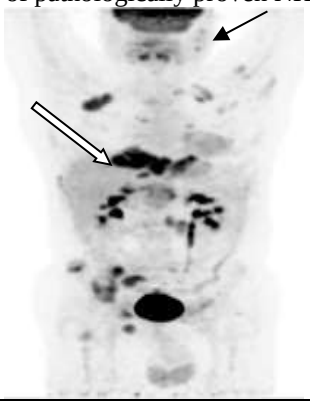

Fig. 4b: whole body MIP PET image.

The whole body PET and PET/CT fused images revealed ^{18}F-FDG avid multiple enlarged amalgamated lymph nodes seen involving the ceoliac, epigastric and peripancreatic lymph nodes groups forming a soft tissue lesion in (Fig.4a&b) Multiple widespread metabolically active supra and infra diaphragmatic lymph nodes seen at: left cervical (arrowed), right axillary and left hilar regions (Figs. 4c-d) as well as left para aortic and right iliac lymph nodes (Figs. 4a&b).

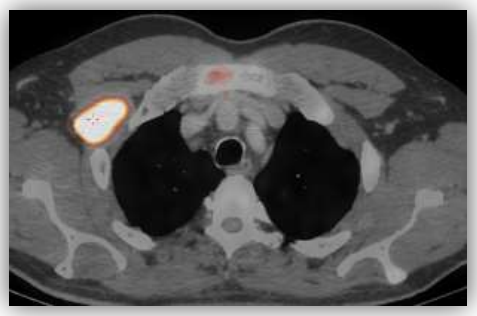

Fig. 4 c: Axial PET/CT fused image of the upper chest.

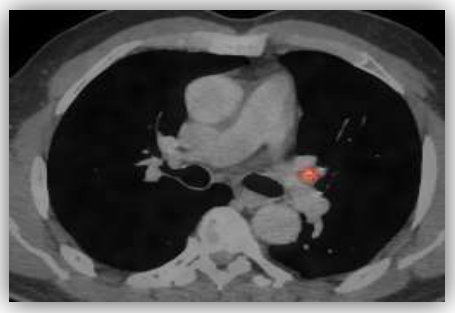

Fig. 4d: Axial PET/CT fused image of mid chest.

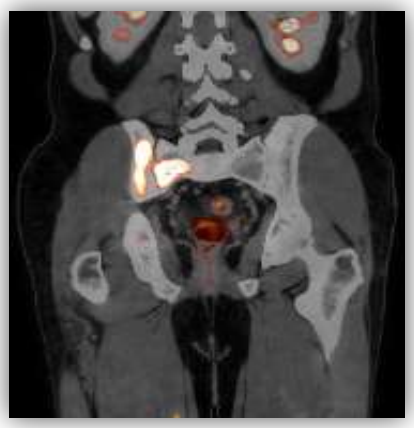

Fig. 4 e: Coronal PET/CT image of the pelvis

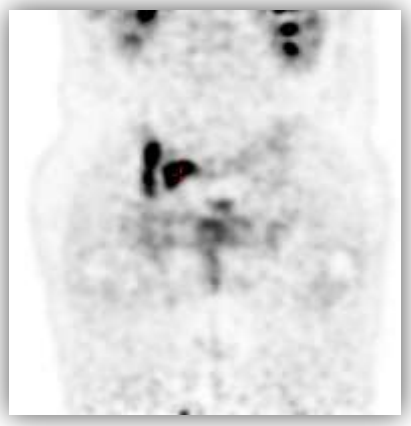

Fig. 4 f: MIP PET image of the pelvis

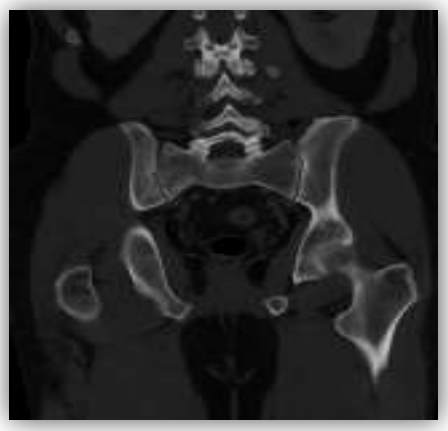

Fig. 4 g: Coronal CT image of the pelvis (bone window).

Fused PET/CT and PET images of the bony pelvis (Figs. 4e&f) revealed focal increased ^{18}F-FDG uptake involving the right iliac and right sacral bone with no corresponding CT abnormalities (Fig. 4g).

Case No. (4): (64) years old male, coming for ***primary staging*** of pathologically proven NHL.

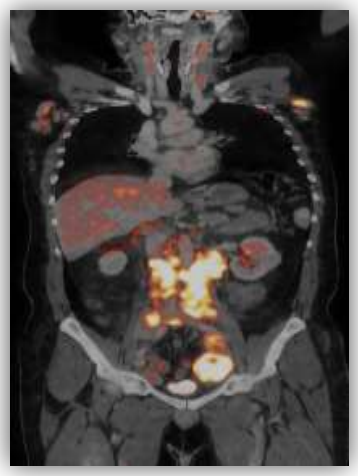

Fig. 5a: whole body Coronal fused PET/CT image.

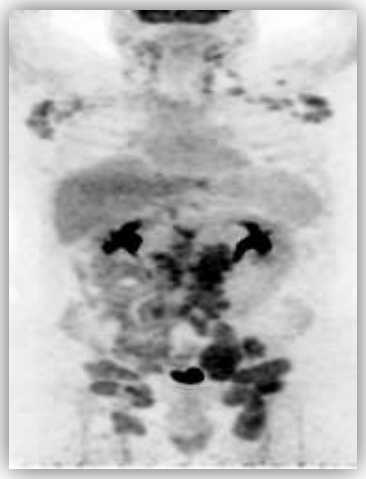

Fig. 5b: whole body MIP PET image.

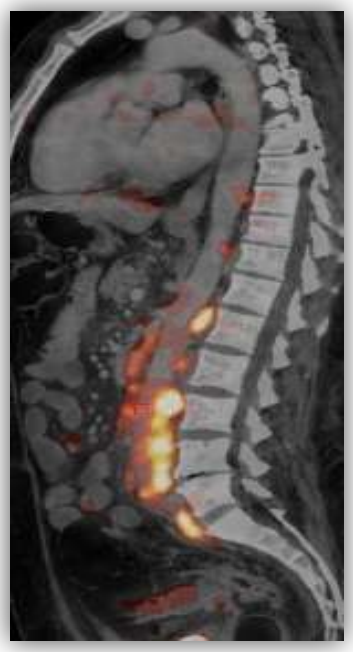

Fig. 5c: whole body sagittal fused PET/CT image

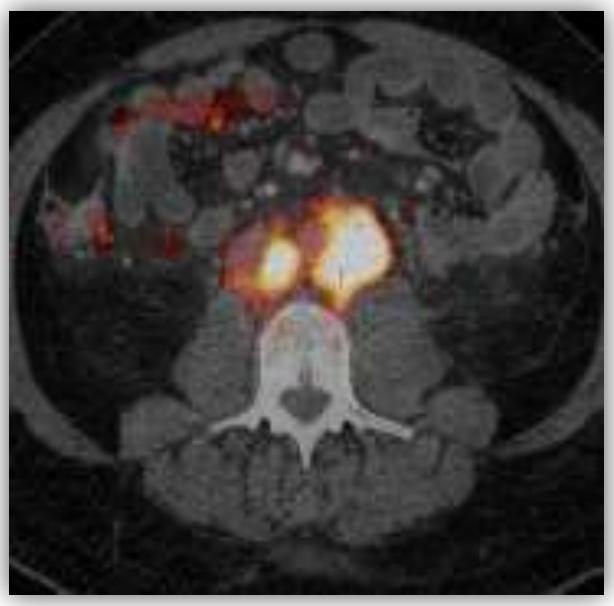

Fig. 5d: axial fused PET/CT image of the lower abdomen

The whole body PET and PET/CT fused images show wide spread supra and infra-diaphragmatic enlarged lymph node groups that show avid ^{18}F-FDG uptake at the following sites: bilateral cervical, bilateral axillary lymph nodes groups (Figs. 5a&b) para-arotic, retro-peritoneal, bilateral iliac and bilateral inguinal lymph nodes groups (Figs. 5a-d).

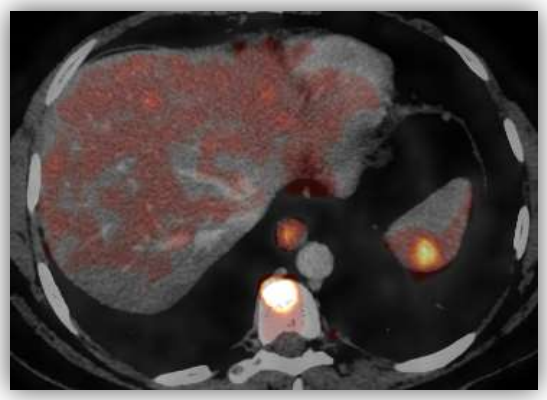

Fig. 5 e: Axial contrast enhanced CT image of upper abdomen al fused PET/CT image

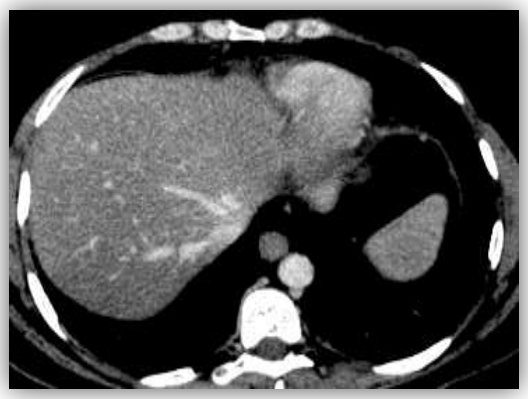

Fig. 5f: Axial PET/CT fused image of upper abdomen

A small ^{18}F-FDG avid was noted at the splenic dome (Fig. 5e) with subtle corresponding faint hypodense focal lesion in CT images (Fig. 5f).

Case No. (5): (50) years old female coming for ***post treatment evaluation*** of Non Hodgkin lymphoma following 6 cycles of chemotherapy.

Fig. 6a: Pre-treatment whole body coronal fused PET/CT image.

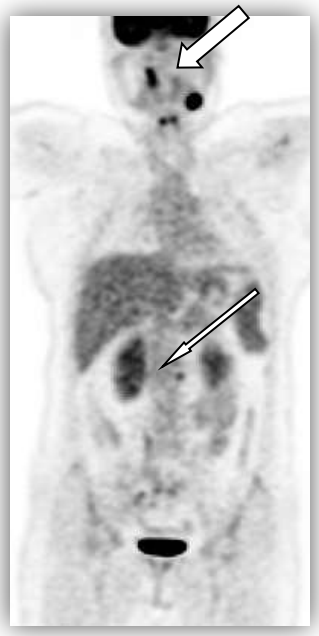

Fig. 6b: Pre-treatment whole body MIP PET image.

In the primary PET/CT (Figs. 6 a&b), there were multiple bilateral cervical FDG-avid lymph nodes (wide short arrow) as well as a small infra-diaphragmatic FDG-avid lymph node (long narrow arrow) that was missed in the primary CT. this upstage the disease from stage II to III.

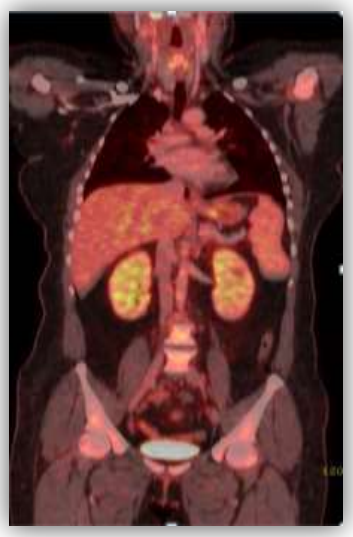

Fig. 6c: Post treatment whole body MIP PET image

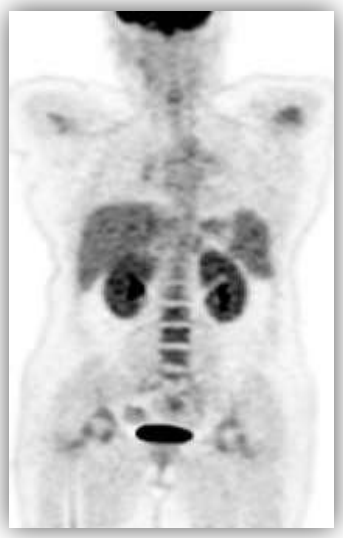

Fig. 6d: Post-treatment whole body coronal PET/CT fused image

The end of treatment PET/CT exam (Fig. 6 c&d) showed evidence of complete metabolic resolution and significant morphological regression of the previously noted ^{18}F-FDG avid multiple cervical and small peri-pancreatic lymph nodes. There are no ^{18}F-FDG avid lymph nodes in the current study.

4. Discussion

Lymphomas are broadly classified as either Hodgkin or non-Hodgkin disease, both are clinically, biologically and pathologically distinct.

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies with different patterns of behavior and responses to treatment. (NHL), it has a far greater predilection to disseminate to extra-nodal sites. Because of the unique anatomy of lymphoid system and because of the physiology of lymphoid cells, which tend to migrate whether they are normal or malignant. The role of lymphoma stem cells in the genesis and maintenance of B cell lymphomas remains speculative ***(Martinez-Climent et al., 2010)***. The age-specific incidence of (NHL) slightly increases over the first 2 decades of life, and increases more dramatically with age, whereas the age-specific incidence of Hodgkin disease is biphasic ***(Workman & Coleman, 2006).*** NHL is divided into (low, intermediate, and high grade). Low-grade has a slow, steady progression and is considered non-curable. High-grade is more aggressive, but responds more to therapy, with long-term remission. ***(Workman & Coleman, 2006)***

In Hodgkin disease the most important distinction to be made is between low/intermediate stage disease (stages I and II) and advanced stage disease (stages III and IV). HD is usually more limited at diagnosis, confined to a few contiguous lymph node regions, without initial evidence of extra-lymphatic involvement. ***(Dessian et al., 2010).***

Unlike most cancers where surgical and medical treatments are utilized, lymphoma is a non-surgical disease and very sensitive to chemotherapy and radiotherapy.Recent developments in treatment have improved the outcome markedly.Careful staging and treatment planning are required to determine the optimal treatment ***(Sethurman et al., 2010)***. The imaging studies for lymphoma diagnosis were primarily anatomical using *(CT) scans.* Anatomical imaging have a lot of limitations including; inability to determine a mass is benign or malignant, to determine if enlarged lymph nodes contain cancer and unable to detect small tumor foci in normal-sized lymph nodes.^{18}F-FDG-PET/CT scan was considered the most accurate tool for the assessment of treatment response and prognosis in patients with Hodgkin lymphoma and aggressive Non-Hodgkin lymphoma ***(Schoder & Moskowitz, 2008).*** ^{18}F-FDG-PET/CT scan enables detection of the increased glucose metabolic rate that is characteristic of most malignant cells. ^{18}F-FDG PET has been demonstrated to be useful for the initial diagnosis, staging, detection of recurrence and evaluation of chemotherapy or radiation therapy responses ***(Tatsumi et al., 2005).*** ^{18}F-FDG has a low specificity it is taken up not only by many malignant tumors but also by sites of active inflammation and some organs physiologically. ***(Rodríguez-Vigil et al., 2006)***

The combination of PET and CT has been strongly advocated representing a unique imaging modality that adds the advantage of anatomical information on a single scanner with perfect image co-registration. Moreover, CT transmission scans provide attenuation correction for PET images resulting in a better image quality at a relatively short scan time. ***(Poeppel et al, 2009)***

There are different methods for assessment of radiotracer (^{18}F-FDG) uptake by normal and pathologic tissues, such as visual inspection, the standardized uptake value (SUV), and the glucose metabolic rate. Visual inspection is frequently used in analysis of PET/CT results by viewing fused PET/CT images. SUVs are used for semi quantification of ^{18}F-FDG uptake. Another method of quantification of dynamic PET results is the more complex glucose metabolic rate calculation.Visual comparison of the described ^{18}F-FDG focus with the blood pool and liver is sufficient to correctly characterize the uptake as low (isointense relative to the blood pool), moderate (nearly isointense relative to the normal hepatic parenchyma), or high (hyperintense relative to the hepatic parenchyma and blood pool). ***(Schwenzeret et al., 2012).***

Diabetic patients usually represent a problem as serum glucose levels greater than 200 ng/dl results in significant changes in ^{18}F-FDG distribution, hyperglycemia leads to competitive inhibition of ^{18}F-FDG uptake into cells. In this study, there were (15) diabetic patients with serum glucose levels more than (200ng/dl), (10) were postponed in order to maintain normal blood glucose level. In the remaining (5) cases we injected one unit of rapid (200cc) saline, and then monitored the blood glucose level, when it was within the accepted range; ^{18}F-FDG was injected one hour later, in two patients there was increased diffuse skeletal muscular uptake, however, no significant effects were noted during the images interpretation. Six patients in this study showed brown fat uptake which was differentiated from ^{18}F-FDG avid lymph nodes by being bilateral and symmetrical in distribution, and its not corresponding to enlarged lymph nodes in the CT images.

Contrast material used in CT (intra-venous) and (oral administration) can potentially generate focal artifacts in the PET image ***(Koppooret al., 2004)***. This would be undesirable outcome, particularly for tumor imaging. The use of oral contrast media is crucial in depiction of bowel wall thickening and is necessary to achieve optimal delineation of abdominal organs. *In this study* we used water as a negative oral contrast agent it was very effective in determining the actual

wall thickening bowel lumen, which is very important in the follow up of patients with gastric or intestinal lymphoma whose response to therapy assessment depends on how much reduction in the bowel wall thickening is achieved. The use of contrast enhanced CT helps in better anatomical localization and characterization of lesions. The intravenous contrast helps in differentiation between the lymph nodes and the vascular structures. It also helps in detection of lymphomatous involvement of the liver, which is very difficult by PET alone, as the normal hepatic uptake is patchy, so correlating hepatic foci of relatively increased ^{18}F-FDG uptake in PET images to focal lesions in the CT images is effective in confirming the diagnosis. We performed triphasic CT scan in three of lymphoma patients with hepatic focal lesions. There were (4) patients *in this study* with renal failure and thus the contrast enhanced diagnostic CT was not performed and un-enhanced CT scans was used, there was no significant difficulty in detection of the involved lymph nodes groups. However the main drawback of using un-enhanced CT for image fusion in cases of hepatic focal lesions.

Raananiet al. (2006) showed that upstaging by PET/CT for both NHL and HD included the detection of increased ^{18}F-FDG uptake in normal-sized lymph nodes (usually less than one cm) as well as in extra-nodal sites, most commonly the liver, spleen, cortical bone, bone marrow and skin, previously missed by diagnostic CT but showing avid ^{18}F-FDG uptake. The latter findings are in keeping with the results of ***Schaefer et al. (2004)*** and ***Hutchings et al. (2004)*** reporting an improved sensitivity for ^{18}F-FDG-PET compared with conventional imaging methods for detecting extra-nodal disease, both in the bone marrow and other organs.

From the (50) patients *in this study* we were able to detect ^{18}F-FDG avid subcentimetric lymph nodes in (6) (12%) patients, these additional sites of lymphomatous involvement would have been missed if staging was done using CT alone. In (4) patients there were no changes in the staging as they were already stage III and IV, while in (2) patients, the detection of the ^{18}F-FDG avid subcentimetric lymph nodes resulted in restaging of these patients from stage (I into II) and stage (II into III). This agrees with ***Rodriguez-Vigil et al 2006*** who reported that PET altered stage in (8%) of patients with untreated NHL and HD who were upstaged from stages (II to III), and in (3) patients from (I to II).

Ngeow et al. (2009) found that PET/CT upstaged (20) (16%) cases, in (13) patients with ^{18}F-FDG-avid splenic lesions; 4 had normal CT findings and would have been missed if conventional CT scans was used for staging alone.In this study, there were (9) patients with splenic involvement, 3 patients showed non-specific splenomegaly by CT images but diffuse ^{18}F-FDG activity higher than that of the hepatic uptake by PET and were reported as splenic involvement. That could have required biopsy for pathological confirmation if it was not combined by PET to confirm the lymphomatous involvement. In another three patients, the spleen was reported normal in size with no focal lesions in CT but foci of increased ^{18}F-FDG uptake were evident at PET. The remaining 3 patients, showed splenomegaly and splenic focal lesions in CT with increased ^{18}F-FDG uptake by PET images.

Paes et al. (2010) reported that bone marrow involvement is indicative of a worse prognosis in patients with lymphoma; it is usually patchy, multifocal and heterogeneous.In this study, there were (7) patients with bone marrow affection by PET that showed multifocal foci of increased ^{18}F-FDG uptake, but with no corresponding CT findings (as bone destruction, osteolytic or osteosclerotic areas). concluded that PET/CT is more sensitive and specific for the evaluation of extra nodal involvement than contrast enhanced CT. We encountered diffuse bone marrow activation in (6) patients in this study, during their interim PET/CT exams; it was typically diffuse, and involving the axial skeleton in a symmetric fashion.

Four (8%) patients *in this study*, had evidence of pulmonary nodules, (3) patients showed ^{18}F-FDG activity and thus changed the staging of these patients while the remaining patient did not show any activity and were reported as benign. *Our study* included [(25) (18.1%)] patients that had CT findings with no corresponding ^{18}F-FDG uptake in the PET images, these included patients with non avid pulmonary nodules and non avid residual lymph node masses.

The CT portion of PET/CT exams plays a crucial role in the response evaluation of lymphoma patients. According to the ***new Cheson criteria 2007***, for response evaluation of lymphoma patients which was applied in this study, if there is residual metabolic activity associated with morphological reduction, the response is either partial response (PR) or stable disease (SD) depending on how much reduction in size is reported by CT, i.e. if the reduction in size was by (>50%), it is considered PR while if the reduction was by ($\leq$ 50%), it is considered SD. So CT has a great value in differentiating patients with PR from those with SD thus sparing the patients with PR from more aggressive treatment and the patients with SD may benefit from changing the treatment regimen.

Group II in this study included (7) patients who ideally performed the staging, interim, end of treatment and follow up PET/CT exams with us. On interpreting their interim PET/CT exams, (4) patients showed evidence of persistent disease; (1) patient was

reported having SD. They either show same size or regression in size of the affected lymph node groups by less than (50%) as assessed by CT but it still showed residual ^{18}F-FDG activity higher than the blood pool activity, so according to the new Cheson criteria, the response was considered stable disease. If response assessment was evaluated by CT alone, reduction in size could have been reported as regressive course. So these patients might have gained the benefit of close monitoring or even changing the treatment regimen. (2) patients showed residual ^{18}F-FDG activity higher than the blood pool activity in the involved lymph nodes groups, with reduction in size by more than (50%), thus were reported as PR. In this study, there were (4) patients with residual lymph node masses on CT after completion of treatment that showed no ^{18}F-FDG activity in the PET images and so they were reported as complete remission (CR). Therefore these patients were spared from un-necessary treatment.

Cronin et al. (2010) Amanda et al. (2011) have convincing evidence that persistent ^{18}F-FDG uptake after two to four cycles of chemotherapy were associated with poor outcome. The response evaluation after the interim PET/CT exams for the (7) patients in group II, revealed (3) patients with complete remission (CR) and (4) patients with persistent disease (1patient was SD,(2) patients were PR and (1) patient was progressive disease PD). After ending their treatment (1-18 months) PET/CT exams were performed; (5) patients showed CR while (2) patents showed persistent disease.

*Group V included (*7) patients that ended treatment and came to detect disease relapse by PET/CT. (4) patients showed disease relapse; (1) of them had evidence of extra nodal disease. From the above data, we can assume that patients with HD usually have a better prognosis than the patients with NHL

In group VI, there were (4) patients with lymphadenopathy of indeterminate histopathologic results came for further characterization of their nature. The PET/CT helped in the suggestion of malignant nature of these lymph nodes by their avid FDG uptake, with SUV max reaching up to (12) in some lesions. This helped in guiding the biopsy by suggesting the most significant lesions with higher metabolic activity to be biopsied. And eventually their biopsy results were confirmed as lymphoma.

Combined PET/CT facilitates the separation of normal physiologic uptake from pathologic uptake, provides accurate localization of functional abnormalities, and reduces the incidence of false-positive and false-negative imaging studies. The imaging time for a whole-body scan is also markedly reduced, enhancing patient comfort and convenience.

Finally, combined PET/CT using ^{18}F-FDG is the best oncologic non invasive imaging modality with indispensable role and valuable application in management of lymphoma. It is very efficient with least possible pitfalls and false results compared to either of its component alone. It is taking its place as the standard imaging modality for lymphoma assessment providing a new vision to management and tailoring treatment plan for each individual patient according to their interim PET/CT responses to their therapeutic regimens. It will have an impact on the national comprehensive cancer network (NCCN) guideline recommendations ***(Zelenetz et al., 2010).***

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