

ONCOLOGY, ORIGINAL ARTICLE**The Comparative analysis of PET/CT and Contrast CT in the Evaluation of Patients with Lymphoma****Khalifa, N. * and Fawzy, A. ****

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ABSTRACT

PET/CT combines functional and morphologic data and increases diagnostic accuracy in a variety of malignancies. Positron emission tomography (PET) imaging with 18-fluoro-2-deoxyglucose (FDG) is used increasingly for the initial evaluation and staging of patients with Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). The number of nodal areas involved is a new prognostic factor as demonstrated in the Follicular Lymphoma (FL) International prognostic index (FLIPI), and their use may be useful for the NHL and HL⁽²¹⁾. The aim of this study is to compare the value of PET/CT over conventional CT in the evaluation of patients with lymphoma for staging or restaging after treatment. **Patients and Methods:** 60 patients with diagnosis of HL (42 patients) and NHL (18 patients) in the initial and follow up staging were reviewed in a single tertiary care center to investigate the potential impact of positron emission tomography (PET)/computed tomography (CT) as compared to conventional enhanced CT on the staging of patients with lymphoma. All patients had FDG-PET/CT imaging study, clinical examination and CT scans. The Ann Arbor stage, each nodal site (cervical, axillary, thoracic, abdominal and inguinal), and extra-nodal sites were evaluated on the basis of FDG-PET/CT scanning and were compared with the findings derived from conventional CT.

Results: PET/CT diagnosed 96 nodal regions as positive for lymphomatous involvement and 384 as disease free the same number was also diagnosed by enhanced CT. Staging concordance between FDG-PET/CT and enhanced CT was found in 50 % of cases, false upstaging by CT was found in 18 (30%) of cases, and false down staging was found in 10% of cases. All cases of discordance between PET-CT and enhanced conventional CT were examined for post treatment restaging. The respective sensitivities, specificities, and accuracies were 99%, 100%, and 99.8% for PET/CT, and 70%, 100%, and 94.7% for CT. PET/CT performed significantly better than CT ($p<0.001$ for sensitivity and accuracy). PET/CT and enhanced CT correctly identified similar extra-nodal lesions.

Conclusion: PET/CT has a higher sensitivity and accuracy in patients with HL and NHL provides significantly more accurate information compared to conventional enhanced CT for the staging and restaging of patients with lymphoma. Specificity is comparative. Disease occurring in normal appearing lymph nodes or extra-nodal sites can be picked up by PET. or CT.

Key Words: PET/CT•PET•CT•lymphoma staging

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INTRODUCTION:

Lymphoma is a common disease, and positron emission tomography (PET) plays an important role in its management. About 60,000 cases are diagnosed each year in the United States, and about 25,000 patients die each year from lymphoma⁽²²⁾. Malignant Lymphomas are a heterogeneous group of diseases whose treatment and prognosis depend on accurate staging and evaluation of histologic features. Non-Hodgkin's lymphoma (NHL) is more common than Hodgkin's lymphoma (HL). Similarly, the mortality rate is higher in patients with NHL compared with HL⁽²²⁾.

CT has been the main imaging technique used for the staging and follow-up of lymphoma⁽¹⁹⁾. The fact that CT assessment of disease is based on anatomic criteria of size and shape and on abnormal contrast enhancement implies limitations in the depiction of pathologic changes in normal-sized lymph nodes and in the assessment of extra-nodal disease. PET with ¹⁸F-FDG provides functional information, but its main drawback of showing few anatomic landmarks impedes precise localization of sites of pathologic ¹⁸F-FDG uptake^(25, 9).

PET with ¹⁸F-FDG has gained a role in the staging and follow-up of lymphomas, largely replacing gallium as the nuclear medicine study of choice. ¹⁸F-FDGPET has proved useful in the staging and follow-up of Hodgkin's disease and non-Hodgkin's lymphoma (especially more aggressive types), and the widespread use of PET/CT has also increased the sensitivity and specificity using co-registered molecular and morphologic images by allowing them to be obtained on the same scanner without moving the patient^(17,1). Controversy exists about whether to perform PET/CT using unenhanced

low-dose CT (for attenuation correction and anatomic localization of PET uptake only) or using contrast-enhanced full-dose CT (for diagnostic CT information also).⁽¹⁸⁾

PET is used in the following ways in the management of lymphoma: 1) staging of disease; 2) Restaging after therapy; 3) monitoring of therapy; and 4) prediction of outcome.

This study aims to compare the value of PET/CT over conventional CT in the evaluation of patients with lymphoma for staging or restaging after treatment.

PATIENTS AND METHODS:

Sixty patients with biopsy proven lymphoma referred to King Fahd Specialist Hospital were studied between August 2009 and January 2010. The study group comprised of 42 had HL and 18 NHL. All the patients were either undergoing staging (24 patients) or restaging (36 patients) including 6 cases of indolent lymphoma.

All of our patients underwent clinical history, physical examination, laboratory work-up (cell blood count, serum creatinine, urea, liver function tests, lactate dehydrogenase, β_2 microglobulin, and viral serologies), imaging findings (contrast-enhanced full-dose CT, PET and MRI when necessary), iliac crest bone marrow biopsy, endoscopy, lumbar puncture, biopsies, surgery when clinically indicated, response to treatment and follow-up data. Follow-up PET/CT data after 3 cycles of treatment were available for all patients, excepting one who died before that time.

For each patient, the true clinical stage was defined according to the modified Ann Arbor system using the available data.

Ann Arbor NHL staging criteria:

Stage 1	single nodal region or single extra lymphatic organ
Stage 2	involvement of 2 or less than 2 nodal regions or single extra lymphatic organ involvement and adjacent nodes on same side of diaphragm
Stage 3	positive nodal regions on both sides of diaphragm
Stage 4	multifocal involvement with one or less extra-diaphragmatic organ

Clinical follow-up, additional imaging and histology (when necessary) served as the gold standard.

All patients underwent PET/CT and Conventional diagnostic CT of the neck, thorax, abdomen and pelvis were performed.

CT PROTOCOL: The patient was placed in supine position on CT table (General electric, Milwaukee, USA). Bowels were opacified with diluted Omnipaque 300mg/ml {Iohexol 647mg/ml} where drinking started at the night before examination (20ml diluted in 1000 water). The stomach was distended on table using two cups of water or diluted Omnipaque. Series 1 of the examination was unenhanced CT started from the skull base and extending to 2cm below the symphysis pubis. For series 2, a bolus of intravenous non-ionic contrast medium 120ml (Omnipaque 300mg/ml) was injected using automated injector at a rate of 3ml/sec. Parameters were 120kV Auto mA was 230, time (sec)=1, FOV=500, matrix 512, slice thickness (mm) =5mm, the increment (mm) =5mm and pitch=2mm. For series, 2 arterial phase was done 36 sec from contrast injection, then porto- venous phase after 45 sec and finally delayed images were taken after 10 minutes so that the patient was evaluated completely for any nodal and extra-nodal pathology or any pathological abnormalities. Soft tissue, lung, mediastinal and bone windows were done. The images were viewed on a workstation as axial and coronal multiplaner reformatted images.

All patients also underwent a PET/CT study that included unenhanced low-dose CT for PET attenuation correction and for anatomic localization. All data were acquired with a combined PET/CT (Gemini; Philips Healthcare) that integrates a 16-detector-row spiral CT scanner. Patients fasted for at least 6 h before undergoing scanning, and blood sugar levels were checked to ensure that there was no hyperglycemia (levels > 7 mmol/l). To prevent muscular radiotracer uptake, we instructed the patients to avoid strenuous activity and to sit without speaking in a dimly lit room before the examination and after injection of the radioisotope. A standard dose of 10 mCi (370

MBq) of ^{18}F -FDG was intravenously injected 45–60 min before imaging. In addition, 1,500 ml of an oral CT contrast agent (diatrizoate meglumine/diatrizoate sodium, 3%) were administered, starting immediately after injection of the ^{18}F -FDG. Scanning was performed from the skull through the mid thigh while the patients were supine with arms above the head, when tolerated. To obtain a precise anatomic correlation between PET and CT images, whole-body scanning was performed with the arms in the same position for both PET and CT. Patients were instructed to breathe shallowly during acquisition of both the CT and the PET images.

Initially, unenhanced low-dose CT was performed with the following parameters: 140 kV, 80 mA, a gantry rotation time of 0.5 s, a collimator width of 2x5 mm, and a section thickness of 5 mm (to match the PET section thickness). PET emission scanning was performed immediately after the low-dose CT, with the identical transverse field of view and in the caudo-cranial direction.

The acquisition time for PET was 5 min per table position. The CT data were resized from a 512 x 512 matrix to a 128 x 128 matrix to match the PET data so that the scans could be fused and CT-based transmission maps could be generated. PET datasets were reconstructed iteratively with an ordered-subsets expectation maximization algorithm and segmented attenuation correction and the CT data. Co-registered scans were displayed using Syntegra software (Philips Healthcare).

Abnormal ^{18}F -FDG uptake was defined as radiotracer accumulation thought to be outside the normal anatomic structures and of greater intensity than background activity inside the normal structures, excluding uptake considered physiologic because it was symmetric or typically located. Only if no pathologic ^{18}F -FDG uptake was seen were CT criteria of lymphomatous disease—based on nodal size, abnormal extra-nodal enhancement (on CT), or structural changes used alone to consider lymphomatous disease. These CT criteria were especially important in types of lymphoma with low or no ^{18}F -FDG uptake.

Quantitative Analysis of FDG Uptake:

For the calculation of SUV, circular regions of interest (15-mm diameter) were placed on consecutive axial images of lesions visually identified to have abnormally increased FDG uptake. In the absence of visual FDG uptake, the biopsy site was used for the determination of SUV. The SUV was calculated as:

$$\text{SUV} = \frac{\text{decay - corrected activity (kBq) / tissue volume (ml)}}{\text{injected - FDG activity (kBq) / body weight (g)}}$$

To minimize partial volume effects and assure reproducibility of measurements, the maximum SUV (SUV_{max}) was used.

^{18}F -FDG uptake similar on follow-up to that seen previously was defined as a non-response to chemotherapy, a reduction of ^{18}F -FDG uptake on follow-up was defined as a partial response to chemotherapy, and the disappearance of ^{18}F -FDG uptake was defined as a complete or full response to chemotherapy. If no pathologic uptake had been seen on the initial staging study, follow-up criteria were based on CT findings (reduction of nodal size or disappearance of extra-nodal lesions).

The surrogate gold standard of Barbara et al⁽⁵⁾ was used for patient assessment to avoid biopsy of every suspicious lesion specifically in patients referred for re-staging. The concordant positive findings of clinical evaluation, CT, PET, and PET/CT were regarded as true sites of disease. Concordant negative findings of clinical evaluation, CT, and PET/CT were regarded as true absence of disease. In cases of discordance between CT, and PET/CT, response to treatment and follow-up data were used to assess the overall accuracy of the patient's disease status. Lesions were considered true positive if abnormalities either persisted on a follow-up PET/CT scan with no interval treatment or resolved on a follow-up scan in patients that had received interval treatment. Conversely, lesions that resolved on follow-up scanning without interval treatment were considered false positive

Image Evaluation:

For every patient, each modality of PET/CT and conventional CT images was evaluated by either of 2 readers separately, (1 experienced radiologist and 1 experienced nuclear

physician). Lesion detection, number of affected groups in 8 anatomic regions, and disease stage were assessed. Agreement between techniques was determined by the figure = 0.92; $P < 0.001$. Lesion detection with each modality was estimated for nodal and extra-nodal sites separately. The possibility of nodal and extra-nodal disease was considered when lesions were clearly present on PET/CT images according to the combined morphologic CT and ^{18}F -FDG uptake criteria. For the analysis, lymph node chains were grouped into 5 broad anatomic regions: cervical, axillary, thoracic, abdominal, and groin (so, each patient has 8 lymph node chains when including the bilateral groups).

The following extra-nodal sites were also evaluated: lung, liver, spleen, gastrointestinal and genitourinary tracts, bone, bone marrow, and other. The findings for each of these sites were graded as positive {2}, indeterminate {1}, or negative {0} for lymphomatous infiltration. Findings were considered indeterminate when the observers were not sure that lymphoma was present. The number of sites affected in each of the 6 anatomic sites (the 5 nodal chains and the extra-nodal site) on unenhanced low-dose PET/CT was compared with that on enhanced conventional CT.

Statistics:

Using the standard of reference, sensitivity, specificity, and accuracy were calculated (7). In addition, comparison between groups was performed using the unpaired *t* test and McNemar test. Correlations were sought using the Pearson correlation. A $p < 0.001$ was considered significant.

RESULTS:

Our study group comprised of 24 women and 36 men. Their mean age is 29.7 years (range, 6-58 years). PET/CT detected cervical 36 positive lymph nodes out of 120 (30%) as compared to 24 cervical lymph nodes in the diagnostic CT (20%), while in the axillary nodes PET/CT showed 18 positive nodes (15%), while the diagnostic CT showed only 6 lymph nodes (5%). In thoracic lymph nodes, PET/CT detected uptake in 12 nodes compared to 36

sizable nodes seen in diagnostic CT. In the abdominal lymph nodes, both modalities showed equal number of lymph nodes, 24 lymph nodes (20%), and the same in the groin

with each modality scoring 6 lymph nodes (5%). In the extra-nodal evaluation, both modalities showed similar detection rate of 6 sites (**Table 1**).

Table 1: FDG-PET/CT and contrast CT findings in the nodal and extra-nodal areas in 60 cases of lymphoma patients

Modality	Nodal Areas										Extra-nodal	
	Cervical nodes (n=120)		Axillary nodes (n=120)		Thoracic nodes (n=60)		Abdominal nodes (n=60)		Groin nodes (n=120)		Liver, lung, etc	
	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
PET/CT	36	84	18	102	12	108	24	96	6	114	6	
Diagnostic CT	24	96	6	114	36	84	24	96	6	114	6	

For each group, the number of sites affected was assessed

The evaluation of the sensitivity, specificity and accuracy of each modality has shown that PET/CT had a higher sensitivity (99%) as compared to the CT at 70% $p<0.001$. Both modalities had a specificity of 100% and a total

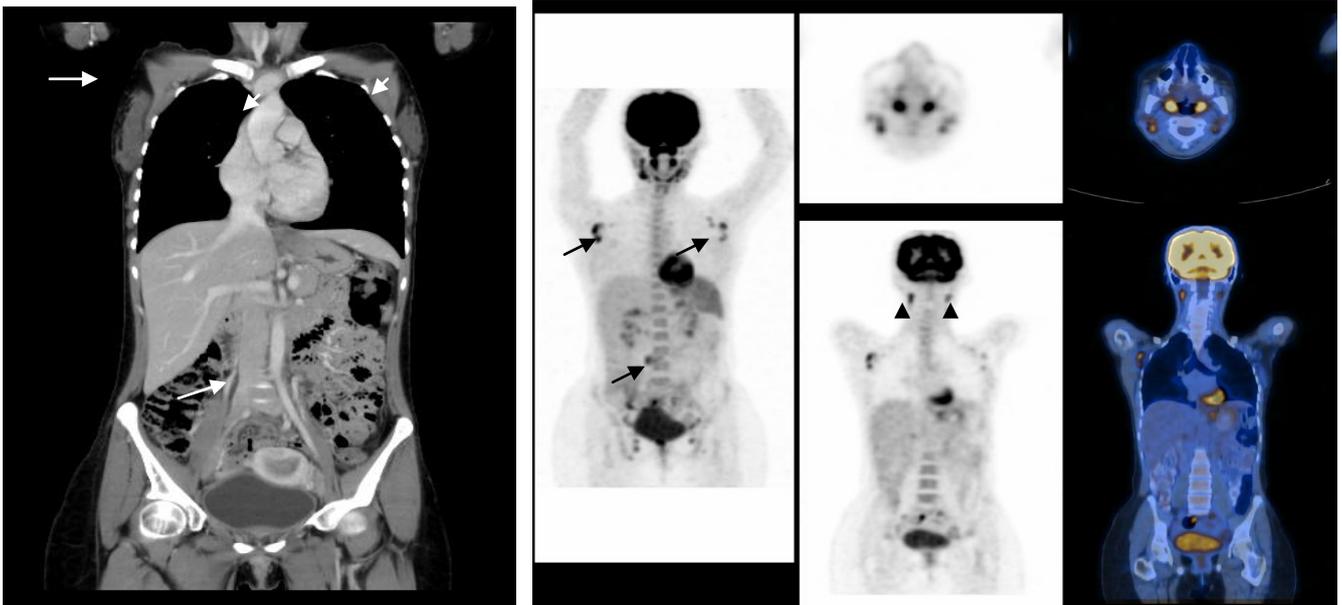
accuracy of 99.8% for PET/CT and 94.7% for the diagnostic CT (**Table 2**). Overall staging using fusion PET-CT in patients with lymphoma was compared with contrast enhanced CT with correction of staging of diagnostic CT according to combined PET/CT and follow up studies (**Table3**).

Table 2: The overall sensitivity, specificity and accuracy of both modalities

Imaging Modality	Sensitivity (%)	Specificity (%)	Accuracy (%)
PET/CT	99	100	99.8
Diagnostic CT	70	100	94.7

Table 3: Number of patients according to the staging of the contrast CT and PET/CT

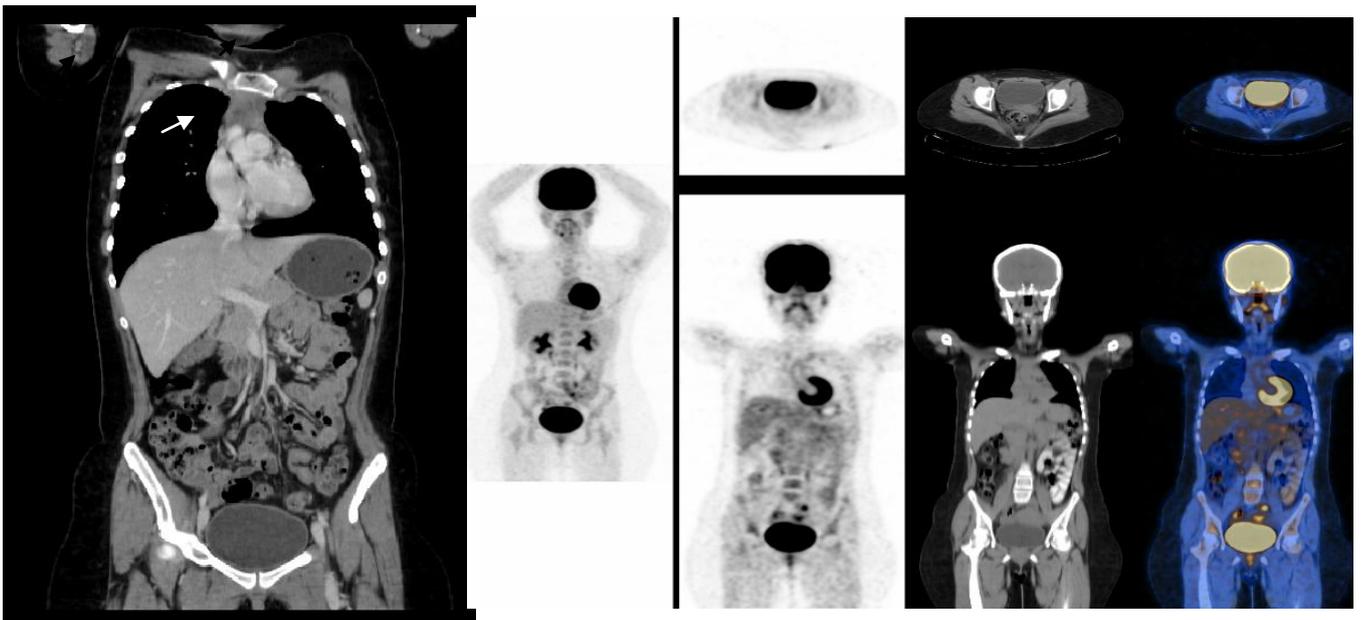
Modality	Stage I	Stage II	Stage III	Stage IV	Disease Free	Concordance	False Up-staging	False Down-Staging
Contrast CT	18	0	18	6	18	50%	18	6
FDG PET/CT	6	6	12	6	30			



(A)

(B)

Case No 1:(A) Coronal reconstructed Porto-venous phase enhanced conventional CT conducted in patient with NHL post treatment showed no sizable axillary thoracic or abdominopelvic lymph nodes (white arrows). (B)PET- CT of the same patient showed still residual bilateral cervical, bilateral axillary, abdominal and iliac lymph nodes with evident ^{18}F -FDG uptake (Black arrows and arrow heads).



(A)

(B)

Case No 2: Pre-vascular space thoracic lymph node and stranding seen by conventional enhanced CT coronal plane equilibrium phase in patient with HL presented in follow up post treatment which was suspected as a residual tumor(white arrows) (A)
 PET- CT of the same patient showed the disappearance of ^{18}F -FDG uptake which was defined as a complete or full response to chemotherapy (B)

DISCUSSION:

The value of FDG-PET over conventional imaging specifically for the staging of indolent lymphoma was reviewed in a number of papers. Jerusalem et al.⁽²⁰⁾ reported that, in 42 patients with indolent lymphoma, PET was able to identify more lymph node areas infiltrated by indolent lymphoma compared to conventional staging procedures. Our study included 60 patients from those 6 cases of indolent lymphoma were recorded. Contrary to the findings of Jerusalem et al.,⁽²⁰⁾ we found no significant difference between the specificity of PET – CT over conventional enhanced CT for the detection of nodal groups with disease (96/480 for both) matching with study conducted by Barbara et al.⁽⁵⁾ However, PET/CT was significantly better in detecting nodal disease metabolic activity than CT modality especially in some cases having sub-centimetric nodes. Our study showed that PET/CT detected the same extra-nodal disease sites as enhanced CT which is not matching with previous studies done by Barbara et al. (5) who proved that PET/CT was able to detect more extra-nodal sites of disease than either CT or PET. This discrepancy is possibly because our study included less number of NHL and indolent lymphoma also most of cases is seen in higher stages or in post treatment follow up staging.

In our study, PET/CT staged more patients correctly than contrast CT. Higher staging acquired by enhanced CT was found in 18 out of 60 cases and down staging was seen in 6 cases (the cases of indolent lymphoma recorded) and all cases were seen at the post treatment staging where the metabolic activity in small sized nodes rather than nodal size was used. However, the differences for overall staging only demonstrated a statistical trend to significance. Najjar et al.⁽²³⁾ reported a similar finding. The combined information of acquired CT and (PET-CT) was more sensitive for staging lymphoma than either modality alone. Disease occurring in normal appearing lymph nodes or extra-nodal sites can be picked up by PET. Conversely, CT can detect disease missed by PET either because of size or because of the

absence of FDG uptake frequently encountered in the setting of indolent lymphoma. The additional value of fused imaging with PET/CT over side by side reading of CT and PET has been reported for multiple malignancies in general (13) as well as specifically for lymphoma (1,18).

Previous studies conducted by Schaefer et al.⁽²⁶⁾ showed that ¹⁸F-FDG PET-CT was superior to CT for M stage but comparable with CT for T and N stages in staging lymphoma (higher stages) and superior to CT for N and M stages in restaging lymphoma. This matches with our results to some extent, however our article was built on the true clinical stage according to the modified Ann Arbor system.

In our study, low dose non enhanced CT was used for attenuation correction of PET, reduction of acquisition time, and localization of hypermetabolic lesions. However some studies done before advocated the need to perform contrast-enhanced and high-resolution CT (29, 14, and 3). Among the latest discussions, there still have been 2 different opinions (11): The work group of Pittsburgh University Medical Center and others, begins the PET/CT study with the acquisition of contrast-enhanced and diagnostic CT and then acquires PET images covering the same axial extent, using the CT data for both attenuation correction and fused PET/CT images (28,27,2). In contrast, other authors obtain 2 CT scans, low- or intermediate-dose unenhanced CT for attenuation correction and, if required, diagnostic intravenous contrast-enhanced CT at the end of the study (29, 10). These authors affirm that intravenous iodinated contrast material produces high-density regions on CT that, when applied as transmission images, lead to artifactual hot spots on the attenuation-corrected image or quantitative overestimation of ¹⁸F-FDG activity (24,12). Nevertheless, recent reports (30, 8) have shown that the presence of intravenous contrast material at normal concentrations actually has little effect on the CT-based attenuation correction factors.

Likewise, the use of oral contrast material at large intestinal volumes and a wide range of

concentrations could lead to overcorrection of the PET data. However, some studies have also demonstrated that there is only a small, clinically irrelevant effect on the standardized uptake value (15, 16). In fact, we advocated the use of oral and intravenous contrast materials to improve the diagnostic capacity of the combined PET/CT study matching with studies conducted by Antoch et.al.⁽⁴⁾. Also, in our opinion it will be useful when doubtful lung lesions are found on the PET/CT study to verify its nature, According to the study conducted by Beatriz et al,⁽⁶⁾ no statistically significant differences was found between the use of unenhanced low-dose PET/CT and enhanced full-dose PET/CT in the depiction of region-based nodal and extra-nodal disease or in the number of positive anatomic sites detected. Their study showed that full-dose PET/CT showed fewer indeterminate nodal lesions (1 patient) than did low-dose PET/CT (3 patients), which may, in our opinion also, increase the radiologist's confidence in lesion detection.

According to Schäfer 2004⁽²⁶⁾ the overall staging using FDG-PET compared with CT was 88% 94% for sensitivity and 86% 100% for specificity. His study included 60 patients of mixed HL and NHL.

The problem with the validation of these studies is that, as we know, the therapy is not surgery in lymphoma. As a result, it is very difficult to validate the imaging procedures by investigating each lymph node that is detected by PET or CT. Most of these studies are based on clinical outcomes, on concordances between PET and CT, and on clinical precisions about disease progression. With these limitations in mind, however, it becomes relatively clear that the sensitivity of FDG-PET imaging is about 10-15% higher than conventional CT imaging (**Table 3**). The specificity is about comparable with CT. Thus, more lesions can be detected with PET than with CT. This applies not only to HL, but also to NHL

Our study had some limitations. The main shortcoming was that our series included relatively few patients. Second, because we did not have histopathologic confirmation for all lesions detected, our findings had to be

evaluated on the basis of follow-up imaging and clinical data. Our recommendation deserves further study to include large population group in different histological lymphoma subtypes with especial concern for indolent lymphoma.

CONCLUSION:

PET/CT has a higher sensitivity and accuracies in patients with HL and NHL. It provides significantly more accurate information compared to conventional enhanced CT for the staging and restaging of patients with lymphoma. Specificity is about comparable Disease occurring in normal appearing lymph nodes or extra-nodal sites can be picked up by PET/CT.

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