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PET/CT and contrast-enhanced CT: making a difference in assessment and staging of patients with lymphoma

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Abstract

Background: The aim of this study is to evaluate the diagnostic performance of contrast-enhanced computed tomography (CECT) and 2-[Fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography combined to computed tomography (18 F-FDG PET/CT) in assessment of lymphoma.

Methods: Hundred patients, pathologically proven as lymphoma, were evaluated by CECT and 18F-FDG PET/CT for initial assessment and staging of the disease. The number of lesions and the disease stage detected by each modality was calculated and further analyzed to be compared.

Results: 18F-FDG PET/CT diagnosed a total number of 545 lymphoma involved regions with sensitivity 96.6%, specificity 98.8%, and accuracy 99% that was higher than CECT which diagnosed a total number of 439 lymphomatous regions with sensitivity 87.5%, specificity 85.7%, and accuracy 88%. Discordant staging by both modalities was found in 23% of the patients. Lymphoma was upstaged by PET/CT in 17% of the patients; with major changes in 12% of them and downstaged in 6% of the patients.

Conclusion: 18F-FDG PET/CT scan has a better diagnostic performance, represented by sensitivity, specificity, and accuracy, than CECT scan in the initial assessment of lymphoma regarding its nodal and extra-nodal lesions that could lead to alteration of disease staging which in turn markedly affecting the decision of treatment regimens.

Keywords: CECT: contrast-enhanced computed tomography, 18F-FDG PET/CT: 2-[Fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography combined to computed tomography

Background

Lymphomas are heterogeneous group of diseases that arise from the constituent cells of the immune system or from their precursors. They are known to arise from virtually any organ or tissue in the body. Lymphomas are broadly classified into two main groups: non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) [1]. Accurate diagnosis, correct staging, and proper therapy are important for successful outcome [2]. Diagnostic imaging plays a critical role in the initial evaluation, monitoring, and follow-up of lymphoma patients [3].

Computed tomography (CT) used to be the imaging modality of choice for staging lymphoma because of its widespread availability and relatively low cost [1]. In combination with powered injectors for rapid bolus administration of intravenous contrast medium used in contrast-enhanced CT (CECT) scan, lymph nodes of 5 mm or less in diameter and extra-nodal lesions with altered enhancement can be identified [4]. At initial staging of lymphoma, determination of nodal involvement by CECT is based on size criteria; if the short-axis diameter is more than 10 mm and/or the long-axis diameter of 15 mm are exceeded. General criteria for extra-nodal involvement are any focal density alterations, abnormal contrast enhancement, or mass lesions involving soft tissues, bones, parenchymal organs, or serosal cavities [5].

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Lymphoma may be restricted to the lymphatic system and/or present as extra-nodal disease, so diverse imaging appearance is expected [6]. Extra nodal lymphomas, seen mainly in NHL, can involve any organ. Secondary extension from a disseminated disease is the most frequent, while isolated primary lesions are possible but rare [7]. Ann Arbor's staging system was commonly used for both Hodgkin's and non-Hodgkin's lymphoma but currently, the Lugano classification was developed to simplify and standardize staging and response assessment [2]. Positron emission tomography (PET) using 2-[fluorine-18] fluoro-2-deoxy-D glucose (FDG) has already been validated to assess patients with different types of malignant tumors, including lymphomas. The principle of the imaging test is based on metabolic changes that reflect fundamental differences in the central metabolic pathways in malignant tissue [8]. 18F-FDG is the most commonly used radiotracer in PET imaging. FDG is an analogue of glucose and the uptake is directly proportional to the glucose metabolism of tumor tissue. Malignant tumors with high glucose metabolism show preferential uptake of FDG as compared to surrounding normal cells [2]. The standardized uptake value (SUV) is a semiquantitative parameter that is widely used in PET analysis and is proportional to the rate of glucose metabolism within the normal range of serum glucose concentrations [9]. Although the metabolic information afforded by PET imaging is invaluable, the quality of obtained data is poor/noisy and limits imaging spatial resolution due to lack of detailed anatomical information, which impedes precise localization of sites with FDG uptake. For this reason, PET scan is often combined with CT imaging, allowing correlation between functional and anatomical imaging [10]. PET is especially helpful in oncology to visualize metabolic processes in malignant tissues. Combined with X-ray computed tomography (CT), it substantially enhances the value of diagnostic results [11]. Treatment is based on a variable combination of chemotherapy, radiotherapy, and immunotherapy, adapted to each type [7].

Methods

The research methodology included the following items:

- Inclusion and exclusion criteria of the studied patients.
- Imaging protocol such as patients preparation, scanning technique and imaging parameters, post scanning instructions, image analysis and data interpretation, and diagnostic criteria of lymphoma by CECT and 18F-FDG PET/CT.

Patients

We retrospectively studied 100 lymphoma patients attended to the radiology department at our institute

from December 2017 to July 2019 for initial assessment and staging of the disease by CECT and 18F-FDG PET/CT scans. The study included adult patients; their ages ranged from 20 up to 70 years distributed as 61 males and 39 females with initial presentation of pathologically proven untreated lymphoma and excluded patients with other malignancies, renal failure, pregnancy, and hypersensitivity to contrast agents.

Imaging method

Protocol

All patients in the study were subjected to full history and complete clinical examination including the clinical stage of the disease. The patients were instructed to fast for 6 h before the scan. Creatinine clearance was checked to be >30 and blood glucose level was ensured to be below 200 mg/dl as non-insulin-dependent diabetic patients were allowed to take small meal with oral anti-diabetic medications then fasting for 6 h but insulin-dependent diabetic patients were allowed to take early breakfast with their normal insulin dose then fasting for 4 h. On the day of scan, diabetic patients with blood glucose level higher than 200 mg/dl were injected rapid acting subcutaneous insulin and re-evaluated 2 h later. If controlled blood glucose level, they were scheduled late in the list to avoid the high FDG uptake by muscles and heart shortly after insulin injection but if not controlled blood glucose level, the patient was scheduled on another day.

Scanning technique and imaging parameters

Intravenous injection (IV) of 2-[fluorine-18] fluoro-2-deoxy-D-glucose 18 F-FDG through IV line with a dose of 0.1 mCi/kg was done. After tracer injection, patient was asked to stay for 60–70 min in a quite dark room covered by warm blankets. No speaking, chewing, or reading was allowed. The patient was taken to the scan room where Siemens Biograph MCT 128 PET/CT exists, as its PET component from Knoxville, USA, and its CT component from Forchheim, Germany. First, a low-dose CT scan at 120 kV, 100 mAs, 0.9 pitch, 5 mm slice thickness, for attenuation correction, was obtained at the range extending from skull base down to upper-thighs. This is immediately followed by a three-dimensional PET acquisition at 3 min/bed position, 6–9 bed positions/patient, field of view 11.4 cm/bed position; obtained at the same scan range. Iterative algorithms, TrueX+TOF ultra HD-PET, 2 iterations, 21 subsets, were used for reconstruction of the PET images. Data were filtered using FWHM 4.0 mm with 3D-Gaussian Kernel and corrected for scatter. After completion of the PET scan, contrast-enhanced CT at 120 kV, 300 mAs, 0.9 pitch, 5 mm slice thickness, and 2.5 mm

reconstruction thickness was done at the same scan range after IV injection of 1.5–2 ml/kg of an iodinated contrast material (Opray 300) using automated injector (Medrad Stellant) with flow rate 4 ml/s. A limited breath-hold technique was used to avoid motion-induced artifacts. Additional maximum inspiration CT scan for detection of lung lesion was performed. The radiation dose was 8.19 ± 0.83 mSv and 13.44 ± 5.14 mSv for PET and CT components, respectively, resulting in a total dose of 21.64 ± 5.20 mSv. That was in agreement with Gomez et al. [12] who mentioned that in 2008, in the USA, the diagnose technique that showed the highest dose deposition in the population was CT scans and Yuhao L [13].

Post scanning instructions

Although the level of radiation, emitting out of the patient after PET scan, is low, it is advised to avoid close contact with children and pregnant women and stop breast feeding for 24 h. If traveling abroad within 48 h is planned, it may trigger the sensitive radiation detectors, so it is advised to have a document stating performing PET scan during the last 48 h. Well hydration and frequent voiding are advised to help flush the radioactive material out of the body.

Image analysis and data interpretation

The attenuation-corrected FDG-PET images, CT low-dose images, as well as contrast-enhanced CT images were automatically fused on True D Siemens software or transferred to Philips Intellispace Portal and OSIRIX fusion workstation. Contrast-enhanced CT (CECT) images are evaluated at axial, coronal, and sagittal reconstructed planes. Maximum standardized uptake value (SUV_{max}) representing the quantitative analysis that measure the degree of FDG uptake at detected lesions was done by applying circular ROI with average diameter 2 cm over the most active part of the lesion. For each patient, 5 lymph node groups including cervical, axillary, mediastinal, abdominopelvic and inguinal groups, spleen, bone marrow, and other body tissues grouped in 9 extranodal sites including lung, liver, rest of GIT, rest of the chest, renoadrenal, muscles, head and neck, breast and skin with subcutaneous tissues were evaluated for lesions at CECT and PET/CT images. So, the total number of examined LN groups was 500 groups/100 patients as the group is considered involved even if a single LN of the group is affected. The spleen is considered involved whatever the number of its lesions, so the total number was 100 spleens/100 patients. The bone marrow was considered involved whatever the number of its lesions, so the total number is 100 bone marrows/100 patients. The other extra nodal lesions

examined in 9 main organs as mentioned before, so the total number is 900 other extranodal organs/100 patients. Then staging (according Lugano classification) of lymphoma is done.

Diagnostic criteria of lymphoma by CECT

General criteria for lymph nodal involvement: if the short-axis diameter is more than 10 mm and/or the long-axis diameter of 15 mm are exceeded. General criteria for extra-nodal involvement are any focal density alterations, abnormal contrast enhancement, or mass lesions involving soft tissues, bones, parenchymal organs, or serosal cavities [5].

All lesions detected on CECT images were re-evaluated on fused PET/CT images for estimation of their SUV_{max} and correlation with FDG uptake by the mediastinal reference background.

Diagnostic criteria of lymphoma by 18F-FDG PET/CT

Any focus of elevated FDG uptake above mediastinal reference background whether on top of an obvious lesion on CECT or not [14].

Four readers in two teams interpreted the same series of patients, with blinding of the imaging reports and the other reviewers' interpretations. The first team is made up of two radiologists that interpret the CECT scan together. The second team is made up of two radiologists with experience in PET/CT reporting.

Data analysis

Data were statistically described in terms of number of lesions, percentages, mean \pm standard deviation (\pm SD), and significance by *P* value when appropriate; sensitivity, specificity, and accuracy of each modality were calculated and compared.

Results

Demographic data

Our study included 100 lymphoma patients where NHL represented 66% of the cases compared to 34% HL. In NHL, male affection (39%) was higher than female affection (27%). Also in HL, male affection (22%) was higher than female affection (12%). The most affected age group by NHL 24% was 50–< 60 years, while the most affected age group by HL 12% was 20–< 30 years (Table 1; Fig. 1).

Contrast-enhanced computed tomography

CECT detected 439 true positive affected sites and 32/471 false positive sites representing a percent of 6.8%, as follows (Table 2; Fig. 2):

- Nodal involvement was truly positive in 266 LN groups with 6 false positive results representing

Table 1 Descriptive statistics of both lymphoma types

Lymphoma type		HL		NHL		Total	
		Num	%	Num	%	Num	%
		34	34%	66	66%	100	100%
Age groups	20-< 30 years	12	12%	4	4%	16	16%
	30-< 40 years	9	9%	7	7%	16	16%
	40-< 50 years	6	6%	16	16%	22	22%
	50-< 60 years	3	3%	24	24%	27	27%
	60-70 years	4	4%	15	15%	19	19%
Sex	Male	22	22%	39	39%	61	61%
	Female	12	12%	27	27%	39	39%

reactive (inflammatory) lymph nodal enlargement and 46 LN groups were false negative.

- Splenic involvement was truly positive in 47 patients with 2 false positive results representing simple cysts. Also, there were 22 false negative results.
- Bone marrow involvement was truly positive in 41 patients with 12 false positive results representing benign lesions including hemangiomas, osteomyelitis, and degenerative changes with 13 false negative results.
- Other extranodal involvement was truly positive in 85 extranodal organs with 12 false positive results, representing hepatic cysts, breast fibroadenoma,

thymic hyperplasia and adrenal adenoma with 25 false negative results.

- The false negative results in all examined sites were proved to be positive lesions by their increased FDG uptake on PET/CT.

18 F-FDG PET/CT

F-FDG PET/CT detected 545 true positive involved sites and 10/555 false positive sites representing a percent of 1.8%, as follows (Table 3; Fig. 3):

- Nodal involvement was truly positive in 312 LN groups with 4 false positive results due to inflammatory process correlated with clinical data and 3 false negative nodal results.
- Splenic involvement was truly positive in 79 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 54 patients with 1 false positive result at the superolateral femoral neck discovered by magnetic resonance imaging (MRI) to be a stress fracture with no false negative results.
- Other extra nodal involvement was truly positive in 100 extranodal organs with 4 false positive results representing chronic tonsillitis and post-

	HL	NHL
Age groups	20-<30 years	4%
	30-<40 years	7%
	40-<50 years	16%
	50-<60 years	24%
	60-70 years	15%
Sex	Male	39%
	Female	27%
Lymphoma type	34%	66%

Percent of patients regarding age group, sex and lymphoma type

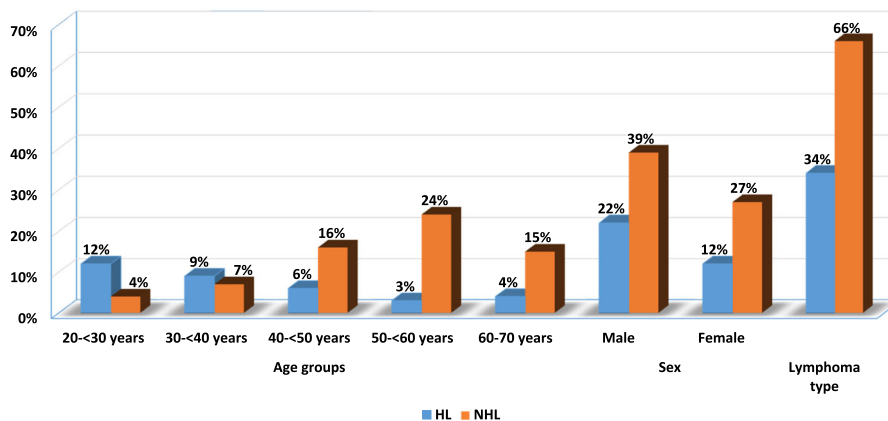


Fig. 1 Descriptive statistics of both lymphoma types

Table 2 Descriptive statistics of the number of lesions detected by contrast-enhanced computed tomography (CECT) scan

Parameters	Number of lesions detected by CECT scan				
	Lymph node groups	Spleen	Bone marrow	Other extra-nodal organs	Total
True positive	266	47	41	85	439
False positive	6	2	12	12	32
False negative	46	22	13	25	106
True negative	182	29	34	778	1023
Total examined sites in 100 patients	500	100	100	900	1600

biopsy subcutaneous axillary inflammatory changes correlated with clinical data with no false negative results.

Regarding the involved groups of lymph nodes by both CECT and 18 F-FDG PET/CT

PET/CT detected more affected LN groups than those detected by CECT with the same order of LN group’s involvement by both modalities, as follows: the most common involved lymph node group was the abdomino-pelvic group by a percent of 74% by PET/CT and 67% by CECT, then the mediastinal group by a percent of 73% by PET/CT and 66% by CECT, followed by the cervical group by percent of 70% by PET/CT and 48% by CECT representing significant *P* value, then the axillary group by percent of 51% by PET/CT and 44% by CECT and finally the inguinal group by percent of 45% by PET/CT and 40% by CECT (Table 4; Fig. 4).

Regarding the involved other extra nodal organs by 18 F-FDG PET/CT

One hundred true positive extranodal organ involvements were detected. The most common involved extranodal organ was the lung 19%, while the least common involved site was the muscles. The organs showing the highest SUV max by PET/CT were lung 44.0, stomach 33.4, submandibular glands 32.7, and kidney 30.8, while the organs showing the lowest SUV max were thymus 2.80, pleura 5.50, peritoneum 6.50, and liver 7.00 (Table 5; Fig. 5).

Regarding diagnostic performance represented by sensitivity, specificity, and accuracy of CECT and PET/CT scans

- For total lesions detection: PET/CT showed higher sensitivity 96.6%, specificity 98.8%, and accuracy 99% than CECT sensitivity 87.5%, specificity 85.7%, and accuracy 88% respectively, as follows:

Parameters	Number of lesions detected by CECT scan			
	Lymph node groups	Spleen	Bone marrow	Other extra-nodal organs
True positive	266	47	41	85
False positive	6	2	12	12
False negative	46	22	13	25
True negative	182	29	34	778

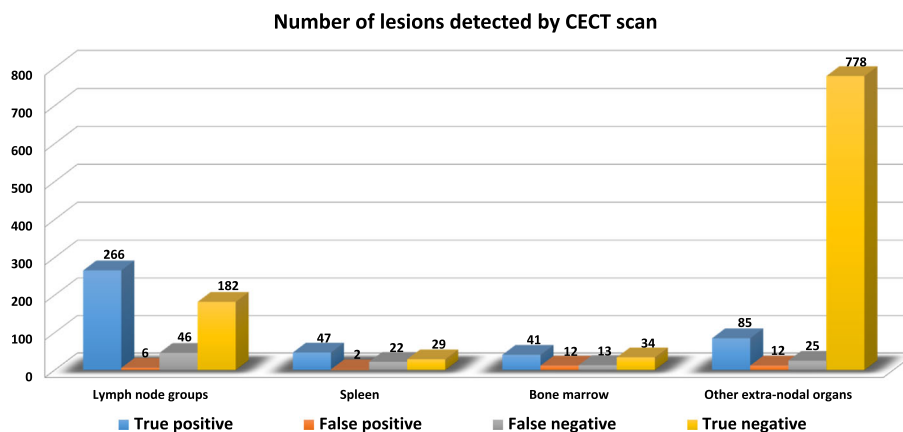


Fig. 2 Descriptive statistics of the number of lesions detected by contrast-enhanced computed tomography (CECT) scan.

Table 3 Descriptive statistics of the number of lesions detected by PET/CT scan

Parameters	Number of lesions detected by PET/CT scan				
	Lymph Node groups	Spleen	Bone marrow	Other extra-nodal organs	Total
True positive	312	79	54	100	545
False positive	4	1	1	4	10
False negative	3	0	0	0	3
True negative	181	20	45	796	1042
Total examined sites in 100 patients	500	100	100	900	1600

- For lymph nodal involvement: PET/CT sensitivity 97.5%, specificity 94%, and accuracy 98% were higher than CECT sensitivity 83.1%, specificity 94%, and accuracy 89.6% respectively with significant difference ($P > 0.005$) (Table 6; Fig. 6).
- For splenic involvement: PET/CT sensitivity 95.2%, specificity 98%, and accuracy 99% were higher than CECT sensitivity 87.6%, specificity 86.6%, and accuracy 76%.
- For bone marrow involvement: PET/CT sensitivity 93.7%, specificity 96%, and accuracy 99% were higher than CECT sensitivity 88.6%, specificity 86.2%, and accuracy 75%.
- For other extranodal organs involvement: PET/CT sensitivity 94%, specificity 96.2%, and accuracy 99.5% were higher than CECT sensitivity 80%, specificity 88.6%, and accuracy 95.9%.

Regarding lymphoma staging according to Lugano classification by CECT and PET/CT

Discordant staging by CECT and PET/CT was found in 23% of the patients. Lymphoma was upstaged by PET/CT in 17% of patients, with major changes in 12%; i.e., upstaging from stages I or II to stages III or IV; and was downstaged in 6% of the patients as follows :CECT diagnosed 8% of the patients as stage I; 3 of them were diagnosed by PET/CT as stage IV which means upstaging with major changes of 3% patients by PET/CT.CECT diagnosed 27% of the patients as stage II; 4 of them were diagnosed by PET/CT as stage III and other 5 of them were diagnosed by PET/CT as stage IV which means upstaging with major changes of 9% patients by PET/CT. CECT diagnosed 28% of the patients as stage III; 5 of them were diagnosed by PET/CT as stage IV which means upstaging of 5% patients by PET/CT. CECT

Parameters	Number of lesions detected by PET/CT scan			
	Lymph Node groups	Spleen	Bone marrow	Other extra-nodal organs
True positive	312	79	54	100
False positive	4	1	1	4
False negative	3	0	0	0
True negative	181	20	45	796

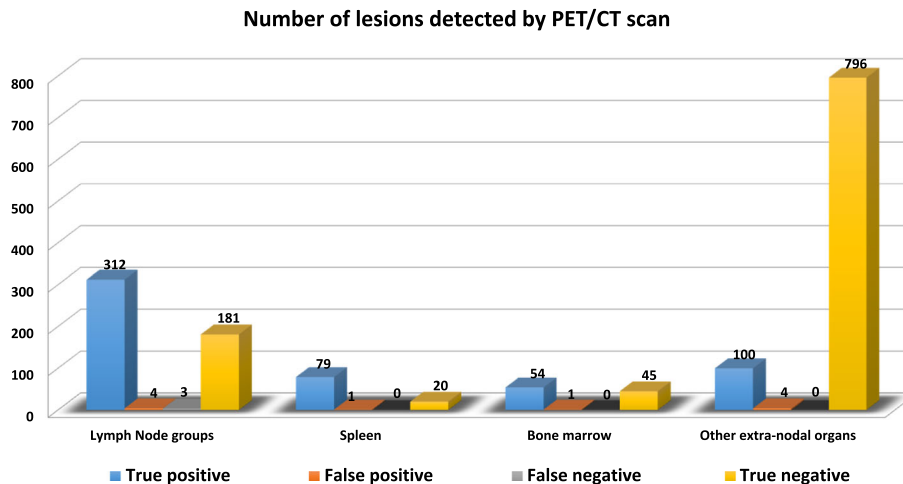


Fig. 3 Descriptive statistics of the number of lesions detected by PET/CT scan

Table 4 Agreement between CECT and PET/CT in detection of involved groups of lymph nodes

Lymph node groups		Involvement of lymph node groups by:				X2	P value
		CECT		PET/CT			
		No	%	No	%		
Cervical	Yes	48	48.0%	70	70.0%	10.004	0.002
	No	52	52.0%	30	30.0%		
Axillary	Yes	44	44.0%	51	51%	0.845	0.396
	No	56	56.0%	49	49%		
Mediastinal and hilar	Yes	66	66.0%	73	73.0%	1.156	0.282
	No	34	34.0%	27	27.0%		
Abdomino-pelvic	Yes	67	67.0%	74	74.0%	1.178	0.352
	No	33	33.0%	26	26.0%		
Inguinal	Yes	40	40.0%	45	45.0%	0.512	0.567
	No	60	60.0%	55	55.0%		

diagnosed 37% of the patients as stage IV; 6 of them were diagnosed by PET/CT as stage III which means downstaging of 6% patients by PET/CT (Table 7; Fig. 7).

Discussion

Many lymphomas are potentially curable with their prognosis depends on the stage and histological

type [5]. 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 diagnosis, staging, and response assessment in lymphoma patients [3]. Integrated PET/CT offers the advantage of combining functional and anatomical information and better attenuation correction

Lymph node groups		Percent of involved groups of lymphnodes by CECT and PET/CT	
		CECT	PET/CT
Cervical	Yes	48.00%	70.00%
	No	52.00%	30.00%
Axillary	Yes	44.00%	51%
	No	56.00%	49.00%
Mediastinal & hilar	Yes	66.00%	73.00%
	No	34.00%	27.00%
Abdomino-pelvic	Yes	67.00%	74.00%
	No	33.00%	26.00%
Inguinal	Yes	40.00%	45.00%
	No	60.00%	55.00%

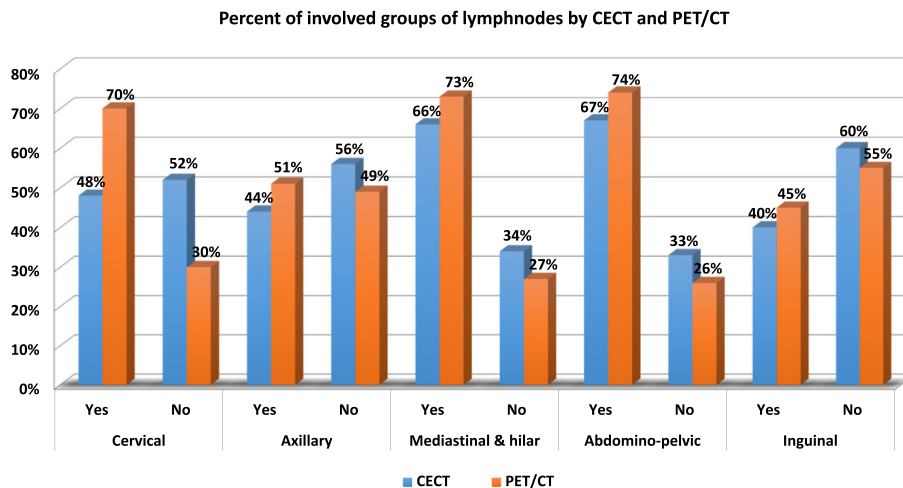


Fig. 4 Agreement between CECT and PET/CT in detection of involved groups of lymph nodes

Table 5 Descriptive statistics of the involved other extra nodal organs by PET/CT and their SUVmax

Involved extra nodal organs	SUV max	Percent of involvement by PET/CT	
High FDG uptake	Lung	44.0	19%
	GIT (Stomach)	33.4	10%
	Head and Neck	32.7 (submandibular gland)	12%
	Reno-Adrenal	30.8 (Kidney)	12%
Moderate FDG uptake	Skin and subcutaneous	27.3	9%
	Breast	25.0	4%
	Muscle	21.1	3%
Low FDG uptake	Liver	7	14%
	GIT	6.5 (peritoneum)	6%
	Chest	5.5 (pleura)	7%
	Chest	2.8 (thymus)	4%

[4]. The purpose of this study is to evaluate and compare the diagnostic performance of 18F-FDG-PET/CT and CECT in the initial assessment of nodal and extra-nodal lymphomatous lesions. For this purpose, 100 patients diagnosed as lymphoma, which proved and classified by histopathology, were initially assessed and staged by CECT and 18F-FDG PET/CT (Figs. 8, 9, 10, 11, 12, 13, 14, 15, 16, and 17).

Regarding demographic data

In this study, the percent of patients having NHL 66% was higher than those having HL 34%; this was agreed with Raanani P et al. [15] whose study stated that the incidence of NHL 68% was higher than that of HL 35%. Also, Mozaffer R and Sadiqa S's [16] study stated that 81.6% of their patients had NHL compared to 18.4% had HL. The same lymphoma type predilection was resulted by Roman E and Smith A [17], while the study of Ricard F et al. [18] was carried out on 50.8% of cases with NHL and 49.2% with HL. In our study, NHL patients showed higher percent of males 39% than females 27%, also HL patients showed higher percent of males 22% than females 12% which emphasizes that male affection by both types of lymphoma is higher than female affection. The same sex predilection was resulted by Roman E and Smith A [17]. In our study, the higher percent 27% of cases was at the age group 50–< 60 years distributed as 24% had NHL and 3% had HL, while the lower percent 16% was at the age group of 20–< 30 years distributed as 12% had HL and 4% had NHL. This was agreed with Rodriguez B et al. [19] who stated that mean age of NHL 52 ± 15 while for HL the mean age was 31 ± 12 .

Regarding total lesions

In our study, PET/CT diagnosed a total number of 545 involved regions with sensitivity 96.6%, specificity 98.8%, and accuracy 99% which was higher than those diagnosed by CECT; 439 involved regions with sensitivity

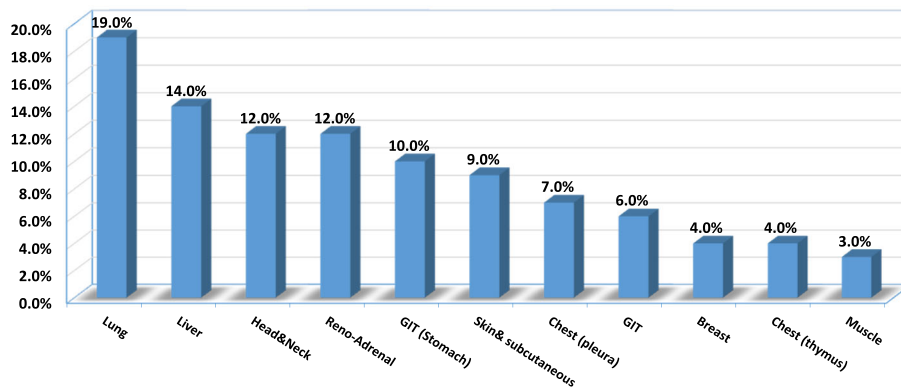
87.5%, specificity 85.7%, and accuracy 88%; la Fougere C et al.'s [20] study showed that PET/CT sensitivity 97% was higher than that of CECT 87.5%, also PET/CT specificity 99% was higher than that of CECT 85.5% as follows.

Regarding lymph nodal involvement

Our study resulted that PET/CT detected 312 true positive nodal group involvement with sensitivity 97.5%, specificity 94%, and accuracy 98% which was higher than CECT that detected 266 true positive nodal group involvement with sensitivity 83.1%, specificity 94%, and accuracy 89.6%, denoting significant difference ($P > 0.005$). Also, there were 46 false negative lymph node groups on CECT that decreased to only 3 groups by PET/CT. This was in agreement with Ricard F et al. [18] who stated that the sensitivity of PET/CT 99% was higher than the sensitivity of CECT 85% and also detected in their study 32 false negative lymph node groups by CECT that was corrected to 3 groups by PET/CT. Kwee T et al. [21] mentioned that some subtypes of lymphoma, namely small cell lymphocytic lymphoma/chronic lymphocytic leukemia may manifest as an increased number of small LNs, which declares that the size criteria used for the morphological assessment of lymph nodes in onco-hematology is insufficient and the metabolic status of lymph nodes by PET scan should be integrated even if their size seems to be normal on CT. The most common involved lymph node group, in this study, was the abdomino-pelvic group, while the least common was inguinal group. In agreement with our study, the most common affected LN group in Mozaffer R and Sadiqa S's [16] study was the abdominopelvic group and the least common was the inguinal group, while the most common affected LN group in Rodriguez B et al.'s [19] study was the mediastinal group and the least common was the abdominal group.

Involved other extra nodal organs	Percent of involvement by PET/CT
Lung	19.0%
Liver	14.0%
Head&Neck	12.0%
Reno-Adrenal	12.0%
GIT (Stomach)	10.0%
Skin& subcutaneous	9.0%
Chest (pleura)	7.0%
GIT	6.0%
Breast	4.0%
Chest (thymus)	4.0%
Muscle	3.0%

(A) Percent of Involved other extra nodal organs by PET/CT



Involved other extra nodal organs	SUV max levels	
High FDG uptake	Lung	44
	GIT (Stomach)	33.4
	Head&Neck	32.7
	Reno-Adrenal	30.8
Moderate FDG uptake	Skin& subcutaneous	27.3
	Breast	25
	Muscle	21.1
Low FDG uptake	Liver	7
	GIT	6.5
	Chest (pleura)	5.5
Chest (thymus)	2.8	

(B) SUV max levels of Involved other extra nodal organs by PET/CT

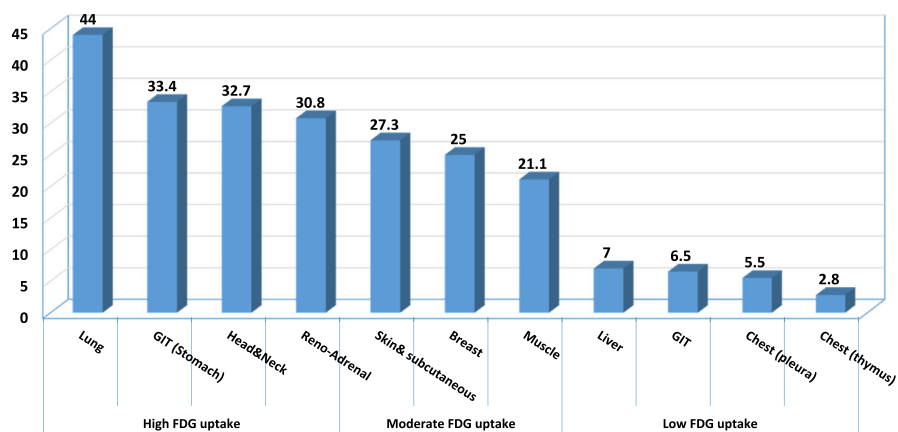


Fig. 5 a Descriptive statistics of the involved other extra nodal organs by PET/CT. b SUVmax of involved other extra nodal organs

Regarding splenic involvement

In this study, splenic involvement was truly positive in 79% of the patients by PET/CT with sensitivity 95.2%, specificity 98%, and accuracy 99% which was higher than CECT that

detected true positive lesions in 47% of the patients with sensitivity 87.6%, specificity 86.6%, and accuracy 76%. There were 22% of the patients with false negative results when assessed by CECT alone that was corrected to zero% by

Table 6 Diagnostic performance of CECT and PET/CT scans

Parameters	CECT			PET/CT		
	Sensitivity	Specificity	accuracy	Sensitivity	Specificity	Accuracy
Lymph nodes	83.1%	94%	89.6%	97.5%	94%	98%
Spleen	87.6%	86.6%	76%	95.2%	98%	99%
Bone marrow	88.6%	86.2%	75%	93.7%	96%	99%
Extra-nodal	80%	88.6%	95.9%	94%	96.2%	99.5%
Total mean	87.5%	85.7%	88%	96.6%	98.8%	99%

PET/CT. Close results were concluded by De Jong P et al. [22] who stated that PET/CT sensitivity and specificity in detecting splenic involvement were 100% and 95% versus 91% and 96% for CECT and confirmed the importance of metabolic status shown on PET/CT to discover splenic lesions with density similar to splenic tissue that could not be differentiated by CECT alone.

Regarding bone marrow involvement

In our study, bone marrow involvement was truly positive in 54% of the patients by PET/CT with sensitivity 93.7%, specificity of 96%, and accuracy 99% which was higher than CECT that detected true positive lesions in 41% of the patients with sensitivity 88.6%, specificity 86.2%, and accuracy 75%. There were 13% of the patients with false negative bone marrow involvement when assessed by CECT alone that was corrected to zero% by PET/CT. Also, the axial skeleton was the most commonly involved. In agreement with our results, Kwee T et al. [21] who mentioned that PET/CT is more sensitive 95% than

CECT 86%. Othman A et al. [23] detected that bone marrow lymphoma mainly affecting the axial skeleton more than the appendicular skeleton.

Regarding other extranodal organ involvement

In our study, PET/CT detected 100 true positive extranodal organ involvements with sensitivity 94%, specificity 96.2%, and accuracy 99.5% which was higher than CECT that detected 85 true positive extranodal organ involvements with sensitivity 80%, specificity 88.6%, and accuracy 95.9%. There were 25 false negative extranodal organ involvements when assessed by CECT alone that was corrected to zero% by PET/CT. In agreement with our results, Ricard F et al. [18] stated that PET/CT sensitivity in detection of extranodal lymphomatous involvement 88% was higher than that of CECT alone 78% and that 9 false negative extranodal results by CECT were corrected to 5 by PET/CT. The most common involved extranodal organs in our study were lung 19%, GIT (mainly the stomach) 16%, liver 14% and renoadrenal 12%. In Das J et al. [22], the most frequently involved

Diagnostic performance of CECT and PET/CT						
Parameters	CECT			PET/CT		
	Sensitivity	Specificity	accuracy	Sensitivity	Specificity	accuracy
Total mean	87.50%	85.70%	88%	96.60%	98.80%	99%

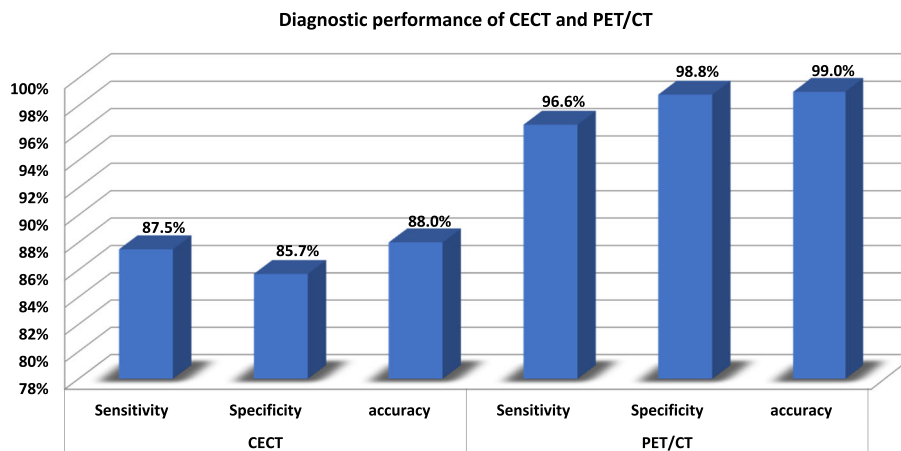


Fig. 6 Diagnostic performance of CECT and PET/CT scans

Table 7 Changes in staging according to Lugano classification between CECT and PET/CT

Lugano stage	PET/CT scan				Total
	I	II	III	IV	
CECT scan					
I	5	–	–	3	8
II	–	18	4	5	27
III	–	–	23	5	28
IV	–	–	6	31	37
Total	5	18	33	44	100

extranodal organs were GIT 14.8% (stomach is commonest site), followed by head and neck region 10% (including tonsils, pharynx, tongue, and orbit), lung 8%, and liver 5%, while Othman A et al.'s [23] study stated that the most common involved extranodal organs were head and neck 18% and GIT 15%. In this study, the organs showing the highest SUV max by PET/CT were lung 44.0, GIT (stomach) 33.4, head and neck (submandibular glands) 32.7, and renoadrenal (kidney) 30.8, while the organs showing the lowest SUV max were chest (thymus 2.80), chest (pleura 5.50), GIT (peritoneum 6.50), and liver 7.00. Othman A et al.'s [23] study resulted that the organs showing the highest SUV max were kidney 73.0, oropharynx 60.0, tonsils 40, and thyroid 37.0, while organs showing the lowest SUV max were pancreas 6.0, peritoneum 8.2, and suprarenal 9.0.

Regarding lymphoma staging according to Lugano classification

Differences in staging by PET/CT and CECT were found in our study. Discordant staging by both modalities was found in 23% of the patients. Lymphoma

was upstaged by PET/CT in 17% of patients; with major changes in 12% (i.e., upstaging from stages I or II to stages III or IV) and downstaged in 6%. In agreement with our results, Ricard F et al. [18] who stated changes in the staging of 20% of the patients with upstaging in 17% and downstaging in 3% with major changes in 10%. Also, Othman A et al.'s [23] study mentioned that 10% of the patients were upstaged while 5% were downstaged after PET/CT. Luminari et al. [24] resulted that PET/CT helped in upstaging of 11% and downstaging of 1% of patients, while Raanani P et al.'s [15] study revealed changes in staging of 39% of the patients after PET/CT with 33% upstaging and 6% downstaging. This change in staging was explained by the higher ability of PET/CT over CECT in detection of involved sites either with normal morphology; as normal-sized lymph nodes or hidden and missed by its isodensity in extra nodal sites, by detection of increased activity in the form of high FDG uptake.

Conclusion

FDG-PET/CT scan should replace CECT in the initial assessment and staging of lymphoma, as FDG-PET/CT scan showed higher sensitivity, specificity, and accuracy which led to alteration of disease staging with marked effects on the decision of treatment regimens.

Limitation of this study

For clear practical and ethical reasons, it was not possible to take biopsies from all nodal and extranodal suspected sites in order to determine a gold

Lugano stage	PET/CT scan				
	PET/CT I	PET/CT II	PET/CT III	PET/CT IV	CECT Total
CECT I	5	0	0	3	8
CECT II	0	18	4	5	27
CECT III	0	0	23	5	28
CECT IV	0	0	6	31	37

Staging by CECT and PET/CT according to lugano classification

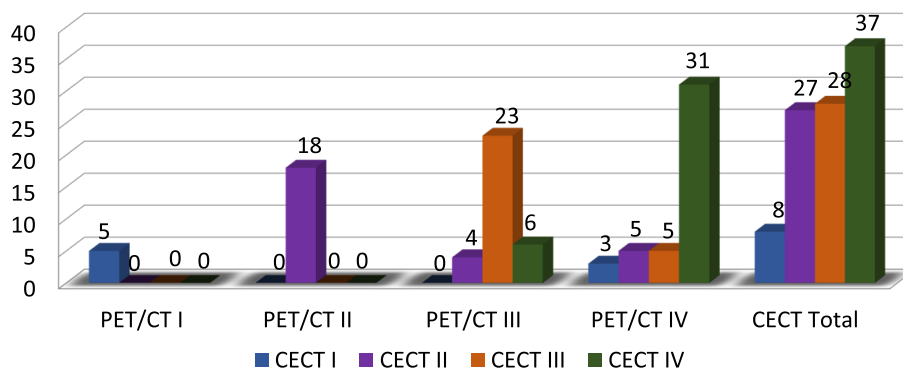


Fig. 7 Changes in staging according to Lugano classification between CECT and PET/CT

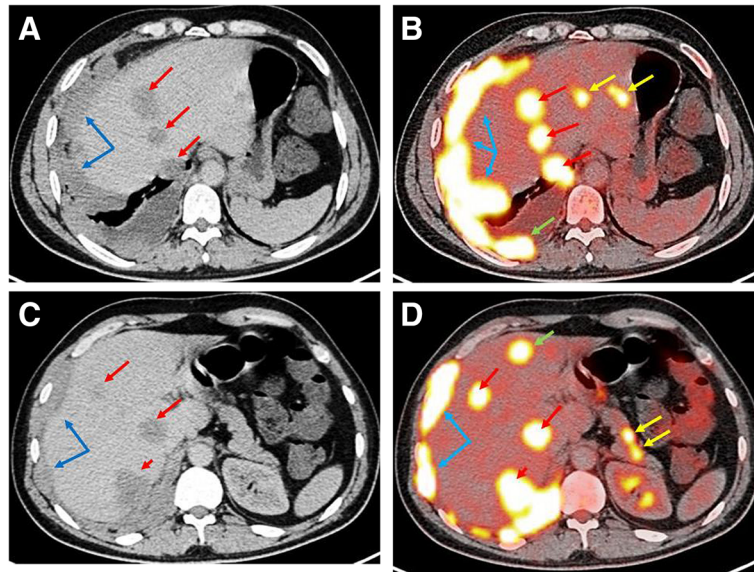


Fig. 8 Male patient 63 years old diagnosed and proven by histopathology as hepatic non-Hodgkin lymphoma. **a** Axial contrast-enhanced CT (CECT) of the abdomen showing three hypodense non enhancing hepatic focal lesions seen at segment VIII (red arrows) and peri hepatic peritoneal nodular thickening (blue arrows). **b** Axial PET/CT showing avid FDG uptake of the three hepatic focal lesions seen at segment VIII (red arrows) and peri hepatic peritoneal nodular thickening (blue arrows) previously noted on CECT, with another FDG avid two hepatic focal lesions seen at segment IV (yellow arrows) and right pleural nodular thickening underlying the pleural effusion (green arrow), not seen on CECT. **c** Axial CECT showing three hypo dense non enhancing hepatic focal lesions; two of them seen at segment VIII (red long arrows) and one seen at segment VII (red short arrow) with peri hepatic peritoneal nodular thickening (blue arrows). **d** Axial PET/CT showing avid FDG uptake of the three hepatic focal lesions seen at segment VIII (red long arrows) and at segment VII (red short arrow) with peri hepatic peritoneal nodular thickening (blue arrows) previously noted on CECT, with another FDG avid one hepatic focal lesion seen at segment IV (green arrow) and pancreatic two lymphomatous focal lesions (yellow arrows), not seen on CECT

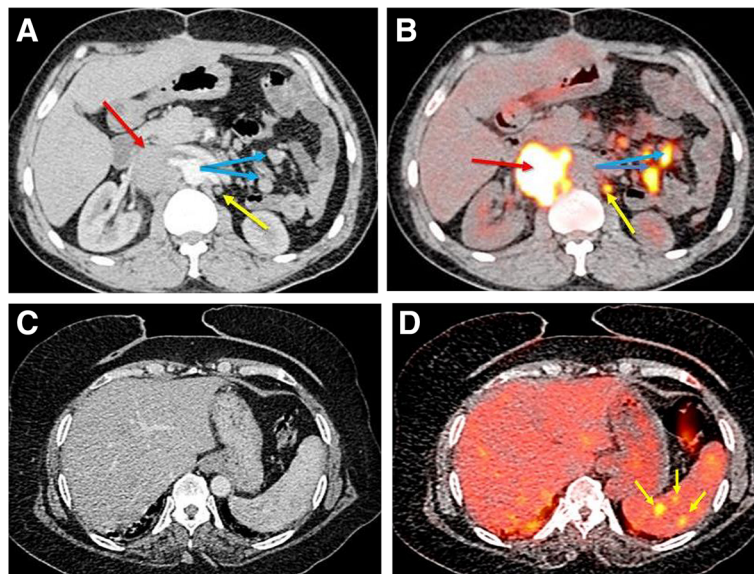


Fig. 9 Female patient 44 years old, diagnosed and proven by histopathology as abdominal lymph nodal Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) of the abdomen showing amalgamated aortocaval lymph nodes (red arrow) and enlarged mesenteric lymph nodes (blue arrows), with a small left paraaortic lymph node 8 mm in its short axis (yellow arrow). **b** Axial PET/CT showing avid FDG uptake of the amalgamated aortocaval lymph nodes (red arrow) and enlarged mesenteric lymph nodes (blue arrows) previously seen on CECT, with avid FDG uptake of the small left paraaortic lymph node (yellow arrow). **c** Axial CECT showing no splenic focal lesions. **d** Axial PET/CT showing increased FDG uptake of three splenic focal lesions (yellow arrows) not seen on CECT

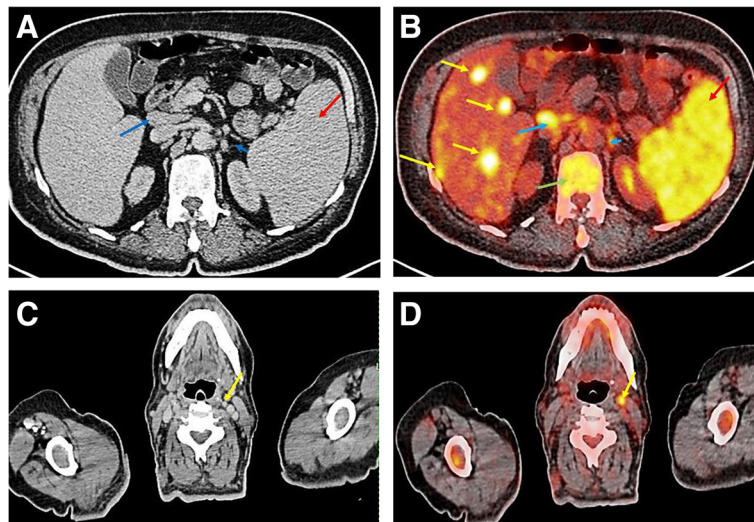


Fig. 10 Male patient 51 years old diagnosed and proven by histopathology as splenic non-Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) of the abdomen showing splenomegaly (red arrow) and enlarged portahepatis lymph node (blue long arrow), with small left paraaortic lymph node 9mm (blue short arrow). **b** Axial PET/CT showing diffuse avid FDG uptake of the enlarged spleen (red arrow), the enlarged portahepatis lymph node (blue long arrow) and small left paraaortic lymph node (blue short arrow) previously noted on CECT, with avid FDG uptake of four hepatic focal lesions (yellow arrows) and bone marrow of the vertebral body (green arrow) not seen on CECT. **c** Axial CECT showing small 7 mm cervical lymph node (yellow arrow). **d** Axial PET/CT showing increased FDG uptake of the small cervical lymph node (yellow arrow)

standard. So, the standard reference was based on clinical data and other monitoring factors including clinical history; physical examination; laboratory work-up such as *cell blood count, serum creatinine, urea, liver function tests, lactate dehydrogenase, b2*

microglobulin, and viral serologies; imaging findings such as ultrasound and MRI when necessary; and iliac crest bone marrow biopsy. This limitation is also inherent in other previously published studies such as Raanani P et al. [15].

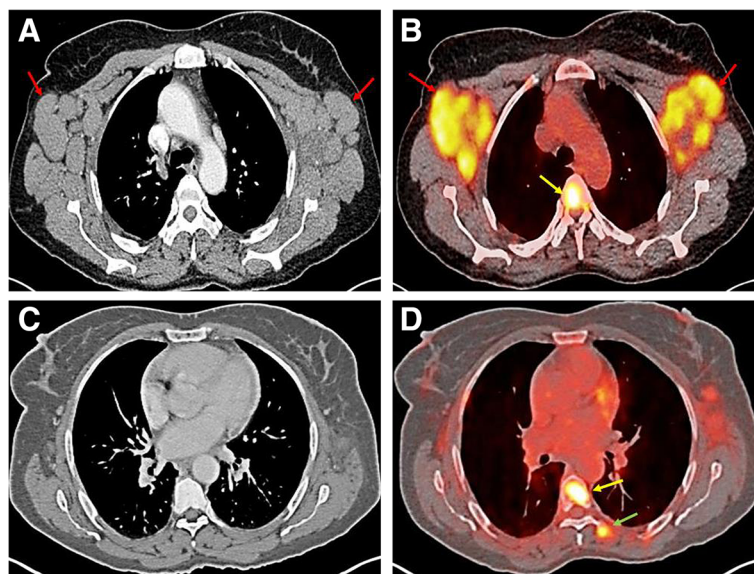


Fig. 11 Female patient 52 years old diagnosed and proven by histopathology as axillary lymph nodal Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) showing bilateral enlarged axillary lymph nodes (red arrows). **b** Axial PET/CT showing avid FDG uptake of the bilateral enlarged axillary lymph nodes (red arrows) previously seen on CECT, with increased FDG uptake of the bone marrow lesion of the dorsal spine (yellow arrow) not seen on CECT. **c** Axial CECT showing no bone marrow or soft tissue lesions. **d** Axial PET/CT showing avid FDG uptake of bone marrow lesion of the dorsal vertebra (yellow arrow) and left paravertebral soft tissue focal lesion (green arrow) not seen on CECT

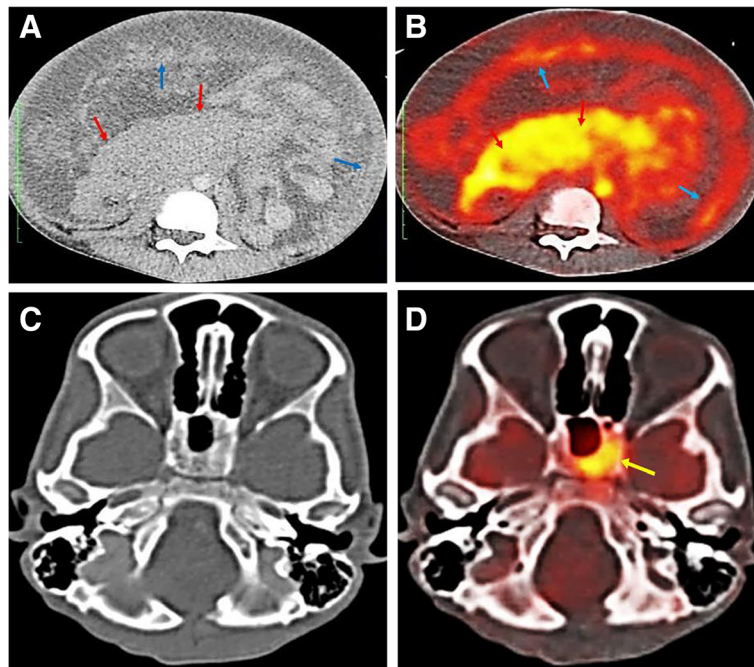


Fig. 12 Male patient 66 years old diagnosed and proven by histopathology as abdominal lymph nodal Non- Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) showing sizable amalgamated paraaortic and mesenteric lymph nodes (red arrows) and peritoneal thickening (blue arrows). **b** Axial PET/CT showing avid FDG uptake of the amalgamated paraaortic and mesenteric lymph nodes (red arrows) and peritoneal thickening (blue arrows) previously seen on CECT. **c** Axial CT of skull base (bone window) showing no lesion could be detected. **d** Axial PET/CT showing avid FDG uptake of lymphomatous focal bone marrow lesion of the left side of the sphenoid bone (yellow arrow) not seen on CECT

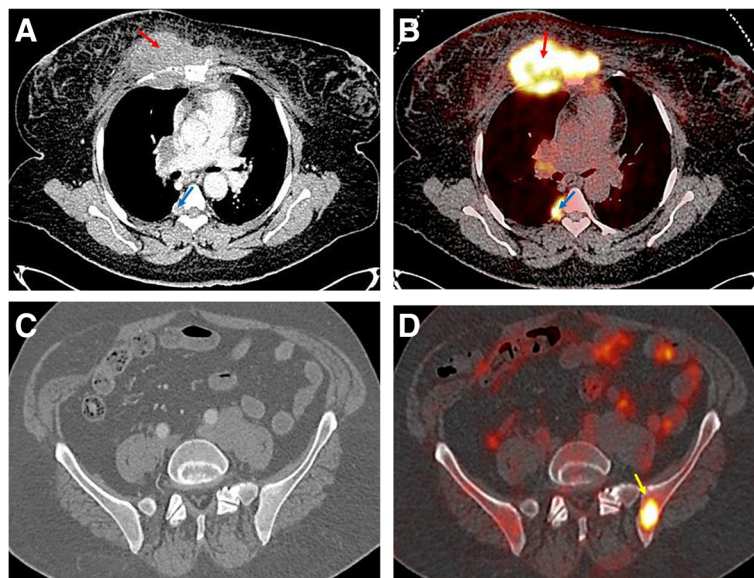


Fig. 13 Female patient 47 years old diagnosed as having anterior chest wall mass lesion, proven by histopathology as non-Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) showing sizable soft tissue mass lesion of the right anterior chest wall infiltrating the underlying bones (red arrow), with small focal right paravertebral pleural thickening (blue arrow). **b** Axial PET/CT showing avid FDG uptake of the anterior chest wall lesion (red arrow) and pleural thickening (blue arrow) previously seen on CECT. **c** Axial CECT of the pelvis ,bone window, showing no pelvic osseous lesion. **d** Axial PET/CT showing avid FDG uptake of focal bone marrow lesion of the left side of the hip bone (yellow arrow) not seen on CECT

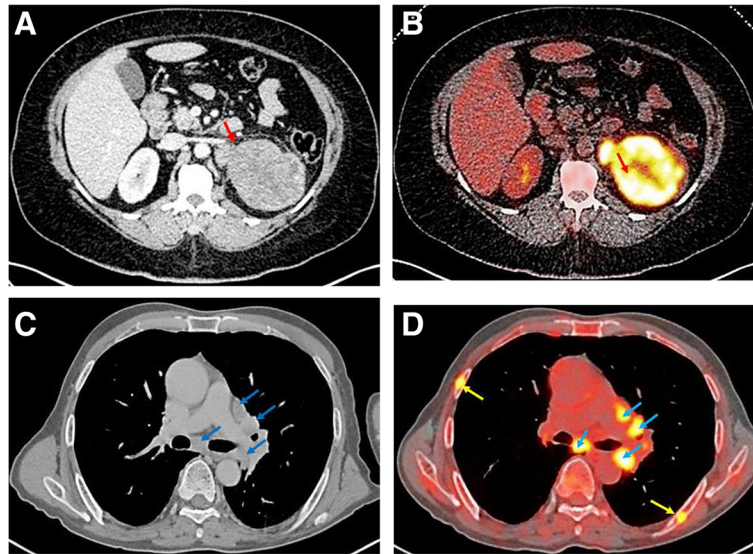


Fig. 14 Male patient 65 years old diagnosed and proven by histopathology as renal non-Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) of the abdomen showing diffusely enlarged hypo dense non enhancing left kidney (red arrow). **b** Axial PET/CT showing avid FDG uptake of the infiltrated left kidney (red arrow) previously seen on CECT. **c** Axial CECT of the chest showing enlarged mediastinal lymph nodes (blue arrows) with no osseous lesion could be detected. **d** Axial PET/CT showing avid FDG uptake of the enlarged mediastinal lymph nodes (blue arrows), with bilateral costal focal bone marrow lesions (yellow arrows) not seen on CECT

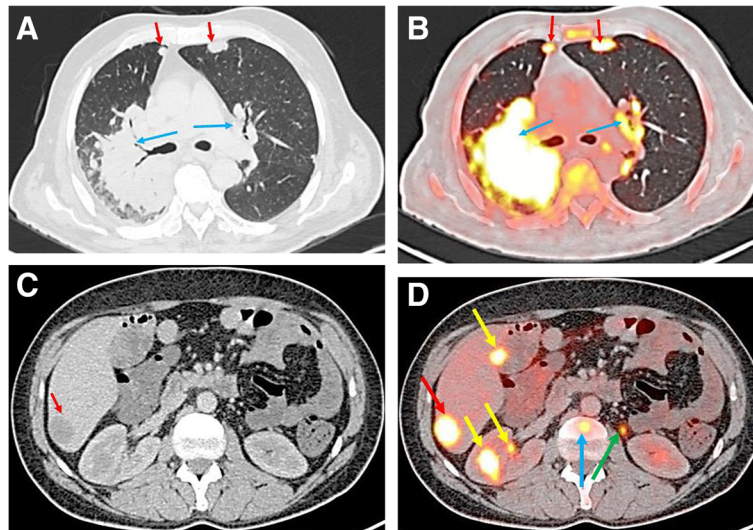


Fig. 15 Male patient 70 years old diagnosed as pulmonary Non- Hodgkin lymphoma which proven by histopathology. **a** Axial contrast enhanced CT (CECT) of the chest, pulmonary window, showing bilateral hilar masses (blue arrows) which is more sizable on the right side that infiltrates most of the right lung field and bilateral anterior subpleural nodules (red arrows). **b** Axial PET/CT showing avid FDG uptake of the bilateral hilar masses (blue arrows) and bilateral anterior subpleural nodules (red arrows) previously seen on CECT. **c** Axial CECT of the abdomen showing single hepatic focal lesion seen at segment VI (red arrow). **d** Axial PET/CT showing avid FDG uptake of the hepatic focal lesion seen at segment VI (red arrow) previously seen on CECT, with avid FDG uptake of: another focal hepatic lesion seen at segment V (yellow long arrow), two right renal focal lesions (yellow short arrows), focal dorsal vertebral bone marrow lesion (blue arrow), and small left paraaortic lymph node (green arrow), not seen on CECT

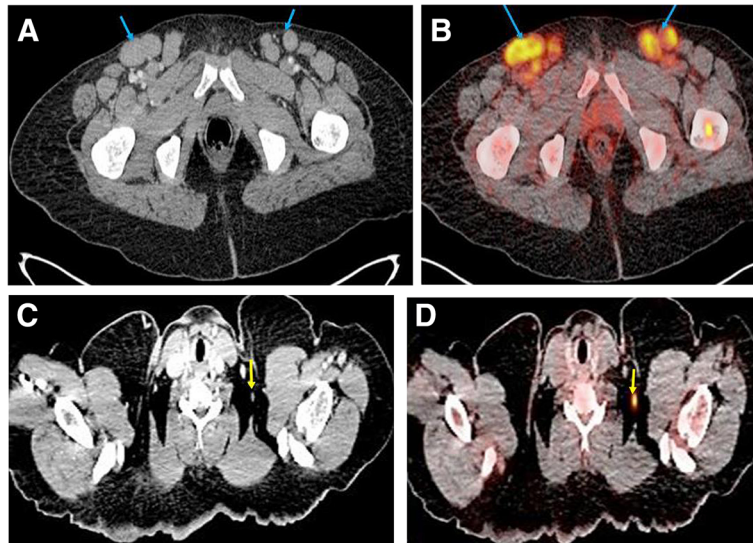


Fig. 16 Male patient 73 years old diagnosed and proven by histopathology as having inguinal lymph nodal non-Hodgkin lymphoma. **a** Axial contrast enhanced CT (CECT) of the pelvis showing bilateral bulky inguinal lymph nodes (blue arrows). **b** Axial PET/CT showing avid FDG uptake of the bilateral bulky inguinal lymph nodes (blue arrows) previously seen on CECT. **c** Axial CECT showing small left cervical lymph node 6 mm in short axis (yellow arrow). **d** Axial PET/CT showing avid FDG uptake of the small left cervical lymph node (yellow arrow)

Recommendations

Novel tools such as the use of Raman spectroscopy (RS) enhanced by using a portable fiber-optic probe, i.e., Raman-enhanced spectroscopy (RESpect) probe, could be leveraged to provide rapid and real-time assessment of malignant lesions as suggested by Agsalda-Garcia et al. [25] that will help to overcome the limitation of

taking biopsies form suspected lesions in order to define a gold standard.

A future study using the same PET/CT scanner to compare low-dose unenhanced PET/CT and full-dose contrast-enhanced PET/CT in lymphoma assessment is recommended aiming at reducing patient radiation exposure.

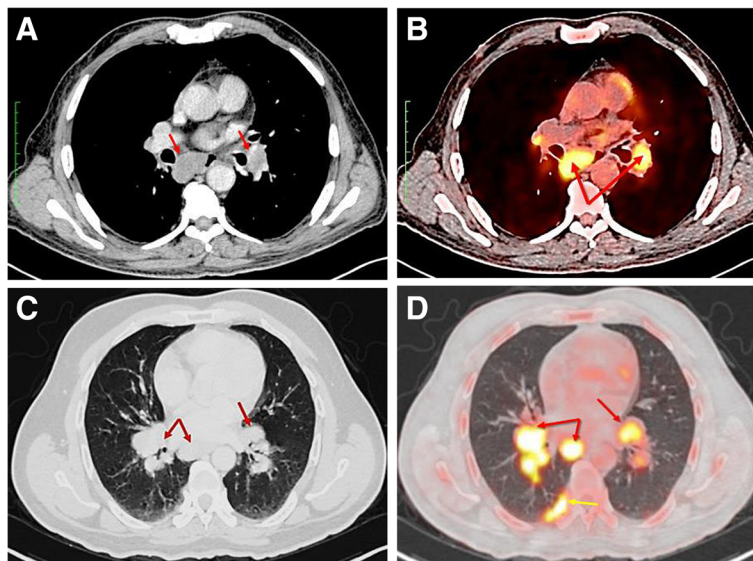


Fig. 17 Male patient 66 years old diagnosed as mediastinal lymph nodal non-Hodgkin lymphoma which proven by histopathology. **a** Axial contrast enhanced CT (CECT) showing enlarged mediastinal and left hilar lymph nodes (red arrows). **b** Axial PET/CT showing avid FDG uptake of the enlarged mediastinal and hilar lymph nodes (red arrows) previously seen on CECT. **c** Axial CECT showing enlarged bilateral hilar and mediastinal lymph nodes (red arrows). **d** Axial PET/CT showing avid FDG uptake of the enlarged bilateral hilar and mediastinal lymph nodes (red arrows) previously seen on CECT, with avid FDG uptake of a small focal right posterior pleural thickening, hardly recognized on CECT (yellow arrow)

Abbreviations

NHL: Non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; CT: Computed tomography; PET: Positron emission tomography; FDG: 2-[Fluorine-18] fluoro-2-deoxy-D glucose; CECT: Contrast-enhanced computed tomography; FDG-PET/CT: 2-[Fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography combined to computed tomography; SUV: Standardized uptake value; IEC: Institutional ethics committee; IV: Intravenous injection; HD: High definition; MRI: Magnetic resonance imaging; RS: Raman spectroscopy; RESpect: Raman-enhanced spectroscopy

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Authors' contributions

All the authors share in study conception and design, acquisition of data, analysis and interpretation of data, drafting, and revision of manuscript. All authors have read and approved the manuscript. AAZ, HMM, BAAEM and MMH 1. Substantial contribution to the conception of the study. 2. Substantial contribution to the design of the study. 3. Substantial contribution to the acquisition, analysis of the data. 4. Substantial contribution to the interpretation of data. 5. Substantial contribution to the creation of the final work. 6. Substantial contribution to the study revision. 7. Substantial contribution to the accuracy or integrity of the submitted manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Our study was approved by ethical and scientific committee - Faculty of Medicine - Menoufia University Ref. No. 86/1//9/2016. Written informed consent form was obtained from every patient after detailed explanation of the study.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The authors declare that they have no competing interests.

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