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Impact of 18F-FDG PET/CT Dual Time Point Imaging in Lymphoma Patients with Lung Lesions.

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ABSTRACT:

The aim of: this prospective study was to assess the role of dual time imaging PET/CT study in characterization of the lung lesions in lymphoma patients with lung lesion. **Patients and methods:** The study was conducted on 28 lymphoma patients. Scan 1 (early image) was performed at 50 min and scan 2 (delayed image) at 110 min after FDG IV injection. The majority of final decisions were reached based on clinical and radiological follow up and the minority was pathologically based. SUV max was calculated at early and delayed images. The difference between early and delayed SUV max (D-SUV max) and the retention index (RI-SUV max) were estimated. Then their cut-off values were evaluated using area under the curve (AUC) from receiver operating characteristic (ROC) analysis. Also, the median quantitative analysis for these parameters was used. **Results:** The delayed SUV max cut-off value of 4.9 giving sensitivity of 90% and specificity of 72% (P=0.004). The cut-off value of D-SUV max of 0.55 yielding a sensitivity of 90% and specificity of 78% (P=0.001). Using 7.5% as a cut-off value of RI-SUV max had sensitivity of 80% and specificity of 67% (P=0.04). The delayed SUV max and D-SUV max had AUCs (0.825 & 0.894 respectively) which is statistically greater than of early SUV max (0.789). The D-SUV max has the largest AUC between the four indices. The median quantitative analysis for Delayed-SUV max was 4.9 (P=0.003), D-SUV max was 0.50 (P=0.001), RI-SUV max was 0.75 (P=0.01). **Conclusion:** The delayed time point PET/CT imaging is additive technique with higher sensitivity and specificity to characterize lung lesions in lymphoma patients.

Key words: FDG PET/CT, lymphoma, lung lesions.

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INTRODUCTION:

^{18}F-FDG PET is a functional modality targeting glucose metabolism, which is markedly increased in most malignant tumours including lymphomas. ^{18}F-FDG PET/CT can assess treatment response during two cycles (interim PET) or after completion of therapy as changes in glucose metabolism are much earlier than structural changes. ^{18}F-FDG PET is a well-established modality in the evaluation of nodal and extra-nodal lymphomas **(1, 2, and 3)**. However, many inflammatory lesions such as pneumonia, sarcoidosis, rheumatoid arthritis, etc., also have elevated F-18 FDG uptake in PET, leading to false-positive results **(4-7)**. Moreover, there is considerable overlap between the maximum standardized uptake values (SUVs) of malignant lesions (ML) and benign lesions (BL), causing difficulty in correctly diagnosing F-18 FDG PET data **(8-10)**. Dual-time-point scans may have an advantage to observe the serial change of uptake in the lesions **(11)**. The accumulation of FDG in cells, following its phosphorylation to FDG-6-phosphate by hexokinase, is facilitated by the glycolytic pathway. This biological pathway allows the characterization of tumor biology and also makes it possible to differentiate malignant cells from normal and inflammatory cells. It has now been demonstrated that both inflammatory and infectious disorders have increased glycolytic activity and therefore can mimic malignancy in many settings. However, high levels of glucose transporters and hexokinase in malignant cells contribute to significant accumulation of FDG in cancer cells over time **(12)**.

The extent of FDG uptake and its clearance depend on the time delay between injection of FDG and the acquisition of images of the disease sites. Cancer cells likely contain low levels of glucose-6-phosphatase for de-phosphorylation of FDG-6-phosphate and this could explain the continuous accumulation of FDG-6-phosphate in malignant cells, revealed on second time point images **(13, 14, and 15)**.

Kumar et al. reported that F-18 FDG uptake in malignant cells was related to low glucose-6phosphatase activity, and increased glucose uptake through glucose transporter proteins in these cells. In contrast, such a prolonged period of F-18 FDG uptake is rare in benign lesions or normal tissues **(16)**. Also, ***Gupta et al.*** reported that the influx rate constant was greater in malignant lesions than in benign lesions, and that continuous tracer uptake by malignant lesions was observed in pulmonary tumor **(17)**.

Aim of the work: To assess the role of dual time imaging PET/CT study in characterization of the lung lesions in lymphoma patients with lung lesion.

PATIENT AND METHODS:

This prospective study was conducted during the period between March 2014 - July 2017. Twenty-eight patients of histo-pathologically proven lymphoma were recruited. They were referred to Nuclear Medicine unit of oncology department at National Cancer Institute either at the end of therapy for response assessment or during follow up. Clinical information was extracted from the medical records, including age, sex, methods of diagnosis, detailed pathology, imaging findings.

Inclusion criteria: All types of lymphoma with lung lesions.

Exclusion criteria: Patients with dual pathology, debilitating disease, recent chemotherapy, radiotherapy and corticosteroid therapy.

The findings of PET, CT, and fused imaging were compared with clinical follow-up results for a period of 6-12 months. The evaluation of imaging was performed directly after imaging, and the results were used for further clinical decision making. All patients were informed about the study. The ethical committee of NCI and the radiation safety committee had given approval.

Diagnostic procedure:

FDG PET-CT

Preparation: Patients should fast for 4–6 h before the study, but drink water to maintain good hydration. The fasting blood glucose level was determined. The preferred fasting blood glucose is below 160 mg/dl.

Acquisition: FDG PET-CT study was done using a dedicated PET-CT scanner (GE, PET CT Discovery). This camera integrates a PET scanner with a dual-section helical CT scanner and allows the acquisition of co-registered CT and PET images in one session.

All patients injected a dose of 370-555 MBq of 18F-FDG according to body weight. Scanning started 50 min after tracer injection.

Intravenous contrast agent was administered in most patients.

Initially, patients were examined in the supine position with arms elevated, and CT scanning was started at the same body region with the following parameters: 400 mAs; 120 kV; slice thickness, 3 mm; pitch, 1.5.

The CT scans were acquired during breath holding within the normal expiration position. PET over the same region was performed immediately after acquisition of the CT images (5–7 bed positions; acquisition time, 2-3 min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 5-mm slices applying a standard iterative algorithm.

Image interpretation: Images were interpreted at a workstation equipped with fusion software (advantage Window AW version 5, GE) that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Image interpretation was accomplished by 2 experienced nuclear medicine physicians (one of them of 9 years' experience, the 2nd one of 15 years' experience). The early and delayed studies were interpreted during the same session. Each reader blindly interpreted the results and if the results were discordant, both readers revised the clinical and other radiological data to get a final consensus. The modified Deauville criteria were used to score the lesions; score 1 & 2 were considered negative, score 3 was considered equivocal and score 4 & 5 considered positive. Also, the decision was based on the changes in SUV max between the early and delayed imaging; in decreasing SUV max, the lesion was considered negative, in increasing SUV max, the lesion most probably positive.

For 18 F-FDG PET/CT The maximum standardized uptake value (SUV max) of lesion related F-18 FDG accumulation at 50 min (early SUV max) and 100 min (delayed SUV max) images.

The SUV of a given tissue is calculated with the following formula:

$$\frac{\textit{Tracer activity in tissue } (\mu Ci/gm)}{\textit{Injected radiotracer dose } (mCi)/\textit{patient weight } (kg)}$$

The maximum standardized uptake values (max SUV) were recorded for lesions in each patient (whether the highest or equivocal lesions), after manual application of the volumetric regions of interest on the trans-axial attenuation-corrected PET slices, around the areas demonstrating the greatest accumulation of 18F-FDG and away from any nearby overlapping activity. Spherical 25-30 mm diameter ROI was drawn over the liver where its max SUV was considered reference activity.

A region of interest (ROI) which was manually drawn for SUV max calculation on early PET scans was placed over the area of maximal metabolic activity on the Trans axial slice showing tumor-related increased uptake.

On delayed PET scans, ROIs were placed in identical positions. In addition to RI-SUV max, we tried to evaluate a usefulness of difference between early SUV max and delayed SUV max (D-SUV max) in this study, as a more simple index. The RI-SUV max and the D-SUV max were calculated as follows:

RI-SUV max = (Delayed SUV max-Early SUV max)/ Early SUV max.

D-SUV max = Delayed SUV max-Early SUV max.

These quantitative values were estimated to evaluate the change of tracers in the lesions at 50 and 110 min after the F-18 FDG injection.

Response:

International Harmonization Project Criteria for Assessment of Response to Therapy for Lymphoma [18]:

Complete Response: complete resolution of FDG avid lesions.

Partial Response: >50% decrease in sum or product of diameters of lesions with persistent residual FDG uptake in at least one site.

Progressive Disease: any new FDG avid lesion; >50% increase in sum or product of diameters of previously involved sites with respect to nadir sum or product of diameters associated with abnormal FDG uptake; or new or recurrent bone marrow involvement.

Stable Disease: no complete remission; partial remission, or progressive disease.

Follow up:

Follow up was performed after 6- 12 months either by PET/CT or CT.

Positive Lesion: A lesion was considered as true-positive if its histopathology was positive or if it showed progression at follow-up.

Negative Lesion: if the lesion histopathology was negative or if follow-up examinations showed marked regression (>50%) in the region of concern without receiving any treatment.

False Positive Lesion: On the other hand, the lesion was considered as false-positive if histopathology was negative or if it showed no progression at follow-up sessions.

False Negative Lesion: if positive histopathology and lesion is growing in follow-up.

Statistical analysis: The data were expressed as mean ± standard deviation (SD).

Receiver operating characteristic (ROC) analysis was performed to determine the proper cut-off value for the difference ML and BL.

The overall statistically difference of area under the curves (AUCs) was evaluated with ANOVA. The significant differences were calculated according to the Student t test; $p < 0.05$ was considered significant.

RESULTS:

The study was prospectively collected and conducted on 28 patients of pathologically proven malignant lymphoma referred for evaluation at the National Cancer Institute, Cairo University in the period between March 2014 and July 2017.

Patient: Patients' characteristics are shown in ***Table (1)*.** The age of the patients ranged from 3 to 77 years with mean 33 ± 21.9. 10 of them below the age of 18 years. The study included 16 males (57%) and 12 females (43%). 16 patients (57%) were pathologically proven Hodgkin's disease and 12 patients (43%) were Non-Hodgkin's disease. Regarding the baseline staging, 50% of patients had stage II and 40% of patients had stage IV. 17 patients were assessed at the end of therapy and 11 patients were under follow up.

Table 1: Clinical characteristic of 28 patient of malignant lymphoma with lung lesions.

Age (mean ± SD)	**33 ± 21.9**	
	No.	**(%)**
Gender Male Female	16 12	(57) (43)
Pathology HL NHL	 16 12	 (57) (43)
Staging at diagnosis I II III IV	 1 14 2 11	 (3) (50) (7) (40)

Diagnostic imaging analysis:

The pattern of lung lesions were described as nodular (n=11), reticulo-nodular (n=9), consolidation (n=3), mass (n=4) and cavitary (n=1) ***(Table 2)*.**

Table 2: imaging pattern of lung changes in 28 patients of lymphoma.

Nodular	**11**	**(39.3)**
Reticuo-nodular	**9**	**(32.1)**
Consolidation	**3**	**(10.7)**
Mass	**4**	**(14.3)**
Cavitary	**1**	**(3.6)**

The results of early & delayed PET/CT images were assessed against the final true status which was based on pathologic confirmation (n=3) {2 were benign and 1 was lymphomatous} or radiologic follow-up, for 6-12 months using CT (n=25).

Qualitative analysis:

On the early imaging, 20 cases were considered positive and 8 patients were considered negative. On the delayed imaging, 12 cases were considered positive and 16 cases considered negative. The discordance between early imaging in relation to the pathology/reference standard was found in 12 patients while the discordance between delayed imaging in relation to the pathology/reference standard was found in 2 patients only. The false positive results of the early PET/CT imaging were significantly higher than the false positive results in the delayed PET/CT imaging. Based on a total of true and false results in early and delayed PET/CT imaging, there was significant improvement in specificity in the delayed PET/CT imaging of 88.8% compared to the early PET/CT imaging of 38.8% ***(Table 3 and Figure 1; A,B and C).***

Table 3: The difference between early and delayed PET/CT imaging's.

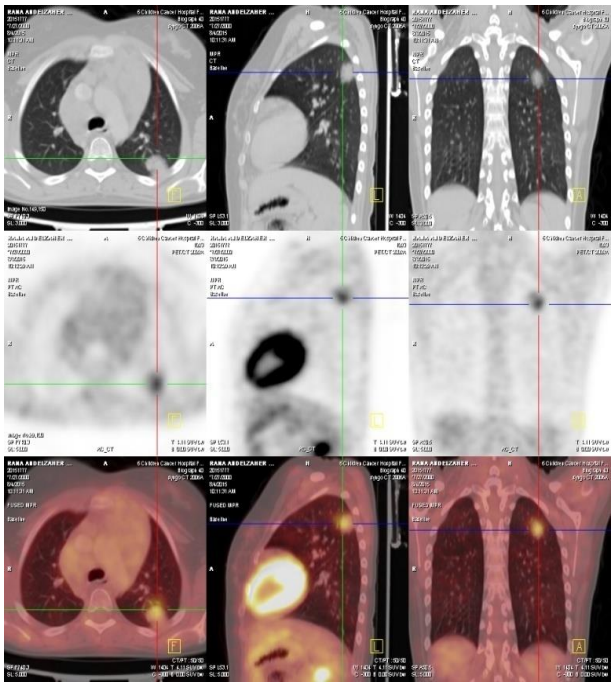
Outcome	Early	Delayed
True positive	9	10
True negative	7	16
False positive	11	2
False negative	1	---
Sensitivity	90%	100%
Specificity	38.8%	88.8%

Quantitative analysis:

- **Median quantitative difference between Early & Dual Time Point PET/CT values:** The median values for SUV max, lesion to mediastinum ratio and lesion to liver ratio were used for lesion quantification based data analysis in early and dual time point FDG PET-CT. There were significant differences between lymphomatous and non-lymphomatous lung lesions in those indices ***(Table 4 & Figure 2).***

Table 4: Early and delayed SUV Quantitative Parameters.

Items	Early	Delayed
SUV max	4.25	4.9
Lesion to mediastinum	2.05	2.5
Lesion to liver	1.65	1.95
D-SUV max	0.50	
RI-SUV max	0.75	



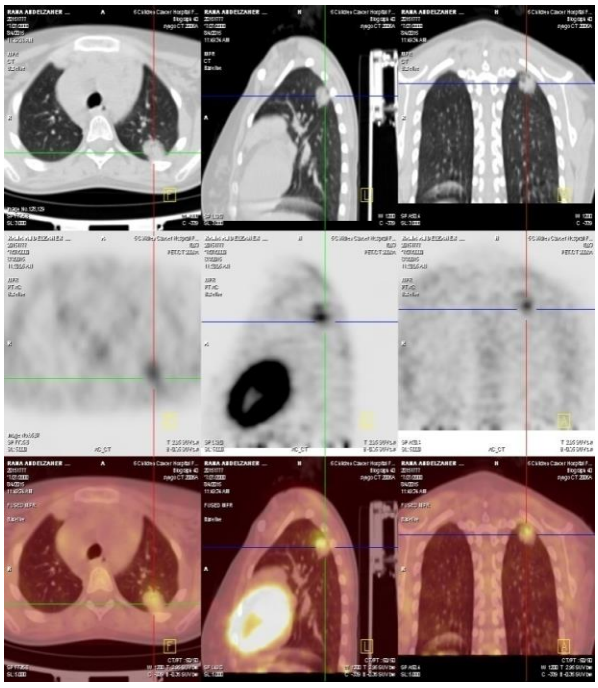
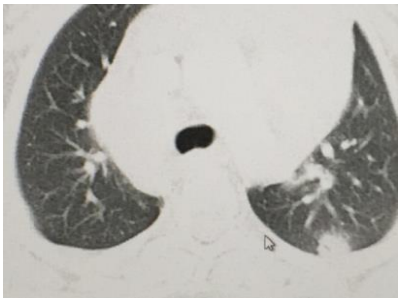
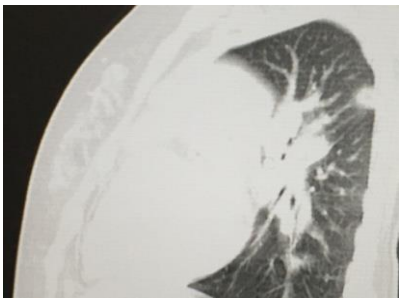


Figure 1 (A): showed FDG avid nodular patch at the posterior segment of left upper lobe with SUVmax~3. (The hepatic reference~4.1).

Figure 1 (B): delayed images, the uptake decreased to~2.8. (The hepatic reference~3.8).





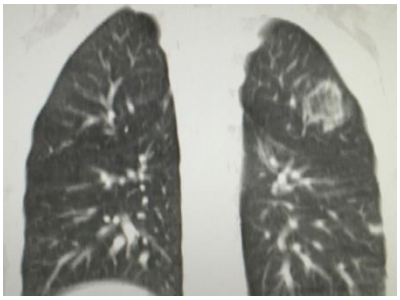


Figure 1 (C): Follow up CT after 3 months (the patient did not receive any treatment) there were stationary course regarding the size (according to clinical and radiological data, the patient was considered true negative).

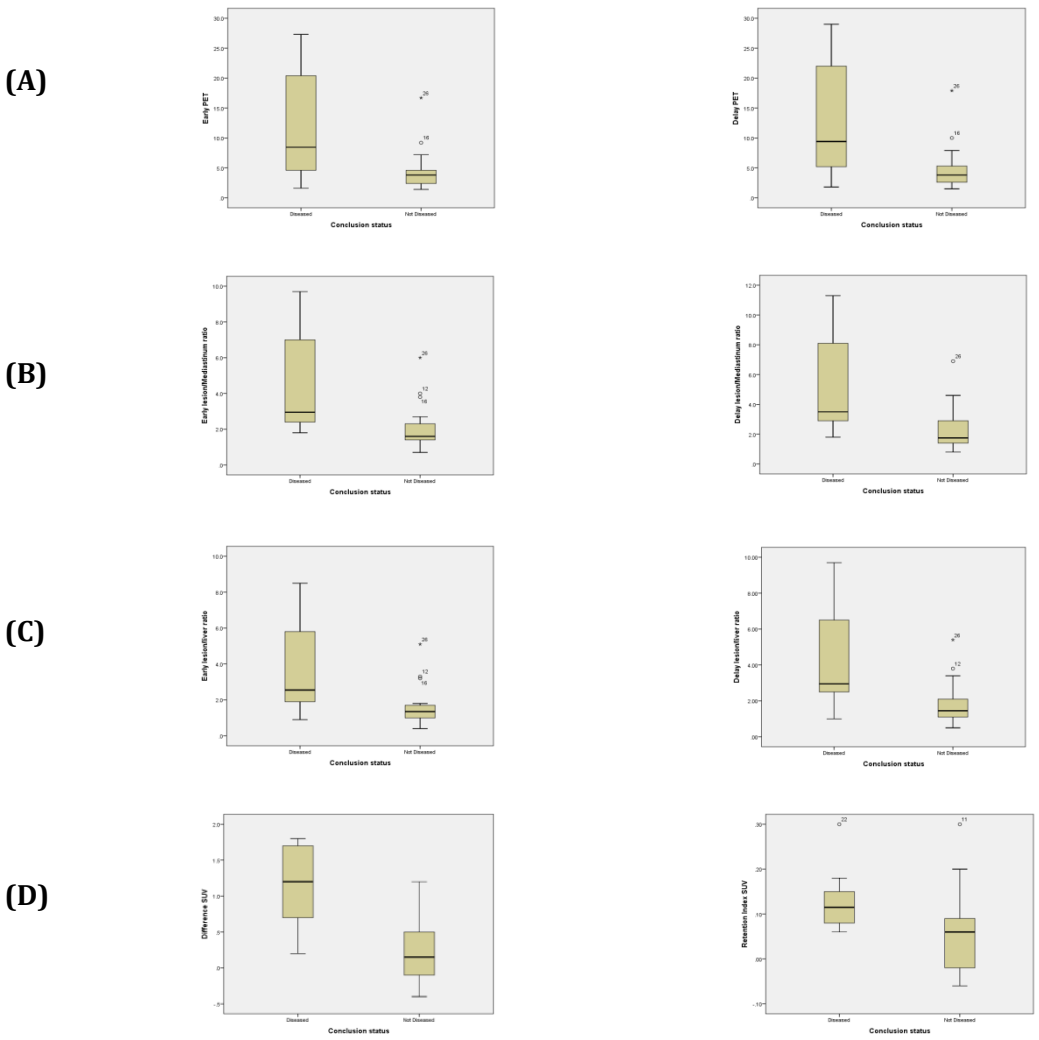


Figure 2: Box and whisker plots showing distribution of Early SUV max, Delayed SUV max **(A)** , Early lesion/mediastinum, Delayed lesion/mediastinum **(B)**, Early lesion/liver, Delayed lesion/liver **(C)**, D-SUV max & RI-SUV max **(D)** among lymphomatous and non-lymphomatous lung lesions in lymphoma patients. The graph showed the distribution of data based on the five number summary: minimum, first quartile, median, third quartile, and maximum [P/0.01 with early SUV max, P\0.004 with delayed SUV max, P/0.003 with early lesion/mediastinum, P/0.003 with delayed lesion/mediastinum, P/0.004 with early lesion/liver, P/0.005 with delayed lesion/liver, P/0.001 with D-SUV max & P/-0.01 with RI-SUV max].

- ROC quantitative Analysis:

A Receiver Operator Characteristic (ROC) curve analysis used to detect a cut-off point in that yield the maximum sum of sensitivity and specificity in evaluation of the different used quantitative indices as summarized in ***Table (5)*.**

Table 5: Different cut off points for DTP-PET/CT in 28 Lymphoma patients with Lung lesions quantification.

	AUC	Cut-off	Sensitivity	Specificity
Early SUV max	0.789	4.5	80%	72%
Delayed SUV max	0.825	4.9	90%	72%
D-SUV max	0.894	0.55	90%	78%
RI-SUV max	0.775	0.075	80%	67%
Early lesion to mediastinum	0.836	2.35	80%	78%
Delayed lesion to mediastinum	0.836	2.5	90%	72%
Early lesion to liver	0.828	1.85	90%	83%
Delayed lesion to liver	0.817	2.4	80%	83%

A) ROC curve for early SUV max:

Using 4.5 as a cut-off point for early SUV max yielding a sensitivity of 80%, and specificity of 72%. This cut off was statistically significant with P-value: 0.013 ***(Figure 3)*.**

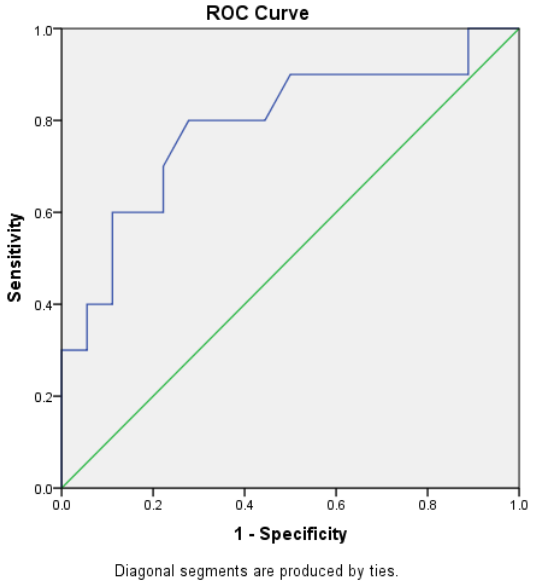


Figure 3: ROC Curve for Early-SUV in Lung Lesions of 28 Lymphoma Patients.

B) ROC curve for delayed SUV max:

The use of delayed SUV max cut-off value of 4.9 provided better differentiation between malignant and benign lung lesions giving sensitivity of 90% and specificity of 72%. The cut-off was statistically significant (P 0.004) ***(Figure 3).***

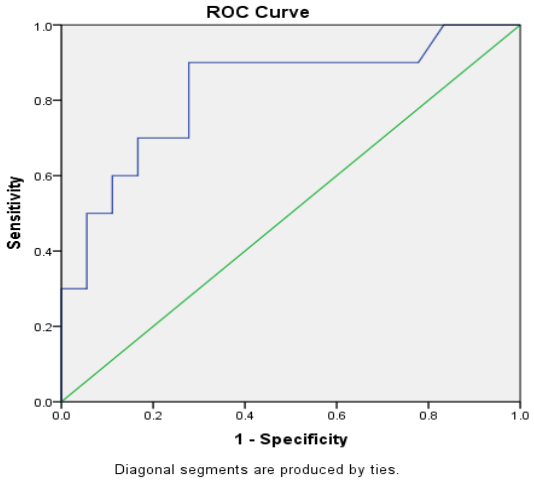


Figure 4: ROC Curve for Delayed-SUV in Lung Lesions of 28 Lymphoma Patients.

C) ROC curve for D-SUV max:

ROC curve analysis marked D-SUV max of 0.55 as cut-off points that discriminate between lymphomatous and benign lung lesions in lymphoma patients. This cut off yielding a sensitivity of 90%, and specificity of 78%. The cut-off was statistically significant (P 0.001) ***(Figure 5).***

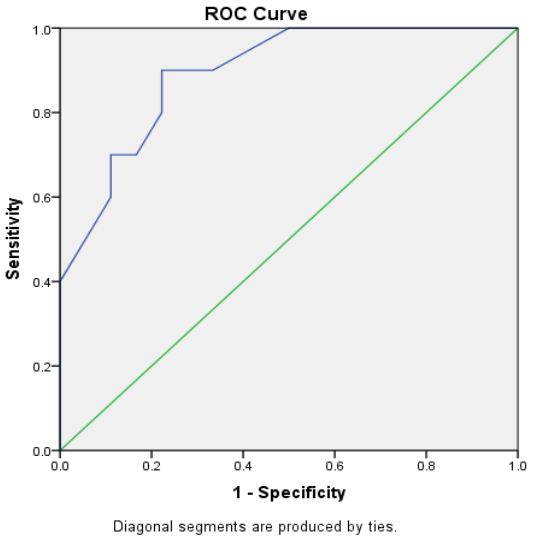


Figure 5: ROC Curve for D-SUV in Lung Lesions of 28 Lymphoma Patients.

D) ROC curve for RI-SUV max: Using 0.075 as a cut-off value of RI-SUV max in differentiation between lymphomatous and non lymphomatous lung lesions in lymphoma patient revealed sensitivity of 80% and specificity of 67%. This cut-off is statistically significant (P 0.04) ***(Figure 5).***

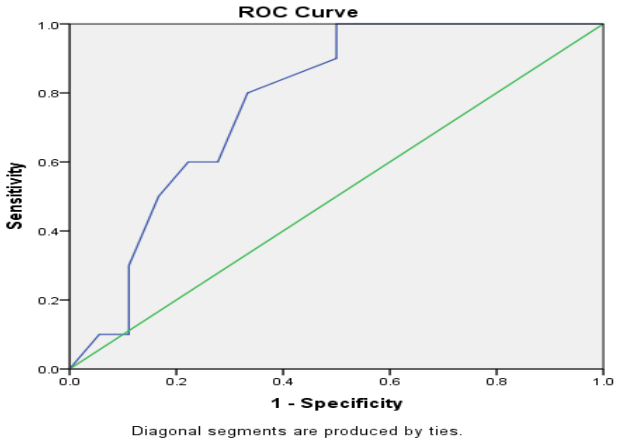
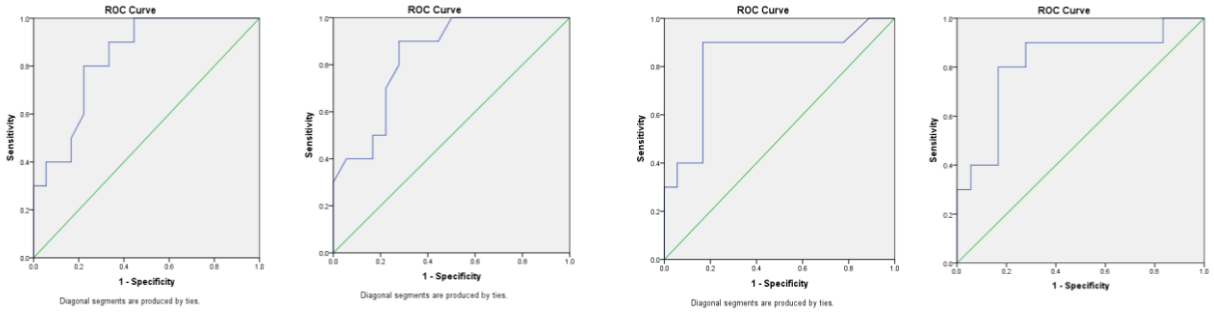


Figure 5: ROC Curve for RI-SUV in Lung Lesions of 28 Lymphoma Patients.



A) **B)** **C)** **D)**

Figure 6 A, B, C, D:
E) Using 2.3 as a cut off for Early lesion/mediastinal ratio showed sensitivity of 80% and specificity of 78% (p 0.004).
F) Using 2.5 as a cut off for Delayed lesion/mediastinal ratio showed sensitivity of 90% and specificity of 72% (p 0.004).
G) Using 1.8 as a cut off for Early lesion/liver ratio showed sensitivity of 90% and specificity of 83% (p 0.005).
H) Using 2.4 as a cut off for Delayed lesion/liver ratio showed sensitivity of 80% and specificity of 83% (p 0.006).

Figure 6 A, B and C: 14 years old female patient with HL (nodular sclerosis), presented with cervical LNS. The patient received 6 cycles of C/TH. 3 months later follow up for assessment of therapy response.

DISCUSSION:

Acute inflammation and infection may have higher FDG activity on delayed imaging, similar to that in malignancy that might due to the different inflammatory cells involved. The underlying rationale of dual time point imaging (DTPI) is that the uptake and clearance depend on the time interval between intravenous FDG administration and imaging [(12)]. Enhanced glycolysis is a unique characteristic of cancer cells which on delayed imaging, still have continuously increasing amounts of FDG trapped in cells in the form of FDG-6-phosphate. While inflammatory tissues with high glucose-6-phosphatase activity will have an early peak followed by a gradual decrease in intracellular FDG retention [(12-19)]. Most normal tissues and benign diseases have decreased background activity and most malignant ones have increased FDG uptake on delayed imaging, leading a higher lesion-to-background ratios, thus higher sensitivity. The specificity of FDG PET imaging is enhanced for diagnostic and prognostic purposes when the dual time point PET/CT has been used for the differentiation of inflammatory and malignant processes [(12)].

The aim of the study was to detect the usefulness of dual time point PET/CT in characterization of lung changes in lymphoma patients.

The present study showed a high potential for delayed quantification in DTP PET/CT images to reduce number of false positive lesions that were detected in early PET-CT imaging. On the other hand, no significant differences were noticed regarding delectability of true positive lesion between early and delayed PET-CT Imaging. Therefore, DTP PET-CT technique improves specificity indices rather than sensitivity indices in evaluation of lymphoma patients. Comparing the results of DTP PECT/CT imaging to the results of the early PET/CT imaging, we found the delayed imaging sensitivity and specificity were 100% &88.8% while the early imaging showed sensitivity and specificity of 90% & 38.8%.

Farghaly et al. evaluated 164 suspicious lesions (20 pre-sacral, 18 lung nodules, 18 Hodgkin disease lesions, 16 rectal lesions, 16 head and neck lesions, 14 hepatic lesions, 14 NHL lesions, 2 mediastinal LNs, 10 focal gastric uptakes, 10 ST lesions, 8 breast lesions, 4 peritoneal nodules, and 4 others). 64 lesions were pathologically confirmed and 100 lesions were confirmed based on 3-6 months follow up.

All the 62 confirmed malignant lesions showed an increase in SUV max in delayed images and resulted in 62 TP lesions, 44 FP lesions, 58 TN lesions and no FN results. The overall sensitivity was 100% of DTP PET/CT in characterizing suspicious lesions. The specificity was 57% in differentiating malignant from benign lesions, the accuracy was 73%, PPV was 59% and NPV was 100% [(20)].

In the present study we calculated the median for Early-SUV max (4.25), Delayed-SUV max (4.9), D-SUV max (0.50), RI-SUV max (0.75), Early lesion/mediatinum ratio (2.05), Delayed lesion/mediastinum ratio (2.5), Early lesion/liver ratio (1.65) and Delayed lesion/liver ratio (1.95).

We found significant difference in the median values of SUV max were detected between lymphomatous and non-lymphomatous lung lesions in lymphoma patients.

Nakayama et al., showed the cut-off of D-SUV max of 1 with sensitivity of 82.6%, specificity of 65.2%, PPV of 80.1% and NPV of 68.8% with P-value <0.005. The D-SUV max was significantly better predictor of ML [(11)].

Costantini et al., found that the degree of overlap became less evident with delayed imaging, likely because the uptake of FDG continues to increase in malignant tissues for several hours after FDG injection, whereas benign lesions show a decrease or remain stable over time [(22)].

In the present study, ROC curve was used to evaluate different used quantitative indices to detect a cut-off point reaching the best compromise between sensitivity and specificity.

In our study, the delayed SUV max and D-SUV max had AUCs statistically greater than of early SUV max.

No significant difference between the AUCs in delayed SUV max and D-SUV max. The largest AUC has found with D-SUV max in the four indices.

The proper cut-off value of D-SUV max of 0.55 yielding a sensitivity of 90 % and specificity of 78 %. Similarly, ***Houshmand et al***. reported the specificity of FDG PET imaging in diagnostic and prognostic purposes was enhanced when the dual time point PET/CT imaging was used for the differentiation of inflammatory and malignant processes [(21)].

The sensitivity reported by ***Matthies et al***., was 100% in the evaluation of pulmonary nodules using DTP F-18-FDG PET protocol [(23)].

CONCLUSIONS:

Dual time imaging in lung lesions in lymphoma patients may be used as additive technique in characterization of lung changes in lymphoma patients. The main limiting factor in our study was the small number of patients and so prospective studies with larger number of patients are advised.

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