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Does FDG PET/CT have Additional Diagnostic Accuracy of Surveillance in Detection of Early Relapse in Non- Hodgkin Lymphoma?

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ABSTRACT:

Aim of the work: is to investigate the diagnostic accuracy of surveillance FDG PET/CT scans in early relapse detection in non-Hodgkin's lymphoma patients coming in complete remission after their primary line of therapy. **Material and Methods:** This prospective study was conducted on 72 patients with NHL (37 males and 35 females) with median age of 52 years. All patients who achieved the first complete remission were scheduled for PET/CT scans every 6 months for the first 2 years. Deauville criteria, SUV max and TLG of all lesions during end of primary line of treatment (if present) and at the time of relapse were measured. **Results:** 56.9% of patients were classified as stage IV. During follow up 30 patients were in complete remission (41.7%), whereas 37 patients had relapse (51.4%), and 5 patients had indeterminate relapse (6.9%). In our study 26 patients of the relapsed group (70.3%) complained of clinical symptoms suspicious for relapsing disease, while only 11 patients (29.7%) did not show clinical manifestations suspicious for relapse before undergoing the follow up PET/CT scan with significant difference (P<0.001). 21 patients of the relapsed group (56.8%) were proved positive by follow up PET/CT as progressive disease, 9 patients (24.3%) was proved by biopsy. 3 patients (8.1%) have undergone conventional imaging CT or MRI with suspicious disease before referral for PET/CT. Only four patients (10.8%) showed regressive course after second line of chemotherapy within close follow up PET/CT. Deauville score at the time of relapse showed 11 patients were presenting with Deauville 4 (29.7%) and the remaining 26 patients showed Deauville 5 score (70.3%).

Diagnostic accuracy of using surveillance PET/CT for early relapse detection in reference to other diagnostic methods showed sensitivity 97.3%, specificity 85.7%, positive predictive value 87.8%, negative predictive value 96.7% and accuracy 91.6%.

Conclusion: Routine surveillance imaging with PET/CT with NHL in CR is valuable in detection of early relapse in symptomatic patients. Metabolic PET/CT parameters including SUV max and TLG are available additive parameters during follow up.

Key words: *PET/CT Surveillance & Early Relapse & Non- Hodgkin Lymphoma.*

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INTRODUCTION:

Lymphoma survivors continue to require post-treatment surveillance for disease relapse and treatment related complications. Despite continued improvement in front-line therapies, a significant portion of patients continues to relapse. Screening for relapse in asymptomatic patients remains a challenge and therefore is an area of intense research as there is considerable variability among different studies. A successful screening approach would identify patients with relapsed disease prior to the development of symptoms, with the theory that early identification of relapse could lead to improved outcomes [(1)].

Our aim of the work is to investigate the diagnostic accuracy of surveillance FDG PET/CT scans in early relapse detection in non-Hodgkin's lymphoma patients coming in complete remission after their primary line of therapy. We aimed also to assess the impact of surveillance FDG PET/CT scans on overall survival for relapsed patients.

PATIENTS AND METHODS:

This is a prospective study that includes 72 patients referred from Oncology department at Kasr Al Ainy hospital Cairo University. All had histo-pathologically proven non-Hodgkin's lymphoma in complete metabolic remission at the end of treatment. Patients were referred for detection of early relapse during follow up. The study was performed in the period between August 2016 and February 2019.

Inclusion criteria:

Adults (age >18 years), both genders, Pathologically proved Non- Hodgkin lymphoma, Availability of conventional imaging, clinical and laboratory tests for staging disease.

FDG PET/CT scan performed at the end of treatment, at least 3 weeks after chemotherapy and preferably 12 weeks after completion of radiotherapy, Post-therapy surveillance, 6 monthly for at least 24 months after the completion of treatment to assist the value of PET/CT in earlier detection of relapse, A written informed consent for the FDG PET/CT scan was obtained from the patients as well, Approval on the protocol by the ethical committee.

Clinical Protocol:

For each patient, we collected base line characteristics, including age, sex, clinical stage, serum LDH, IPI index, date of start and end of primary therapy, Clinical follow-up data, including the date and site of first relapse, All investigations done for patients including radiologic CT or MRI and PET/CT, as well as biopsy if indicated.

FDG PET/CT imaging:

Patient preparation

Patients are fasting at least 4-6 hours prior to the start of the PET study. Adequate pre-hydration was important to ensure a sufficiently low FDG concentration of FDG in urine and for radiation safety reasons. Blood glucose levels should be <150 mg/dl.

During the injection of FDG and the subsequent uptake phase the patient remained seated or recumbent and silent to minimize FDG uptake in muscles. They are instructed not to talk. They could go to the toilet while waiting, preferably after the first 45 min post injection. The interval between FDG administration and the start of acquisition is 45-60 min.

PET/CT scan acquisition:

The patient was positioned with the arm elevated over the head to avoid beam hardening artifacts as well as artifacts caused by truncation of the field of view.

Whole-body FDG PET/CT study was obtained using ingenuity 64 Multi-slice Philips PET/CT scanner.

First, low-dose, CT images were acquired with the following parameters: 120 kV, 26–30 mAs (automatic) dose modulation), 1-sec tube rotation time, pitch of 1.5, and 2 mm slice width (reconstructed to contiguous 5-mm axial slices to match section thickness of the PET images.

PET scanning from mid femur to the base of the skull was performed in six to seven bed positions, with 1-2 min per bed position. Low-dose CT data were used for attenuation correction of the PET images.

The image reconstruction matrix was 144 × 144. Full-dose contrast-enhanced CT of the neck, chest, abdomen, and pelvis with IV contrast agents was also performed to most patients, using the following parameters: 120 kV, 60–160 mAs, 1-sec tube rotation time, pitch of 1.2, and 1.5 mm slice width and 512 × 512 matrix size.

Scan interpretation:

The PET/CT study was done 3 to 4 weeks after the end of treatment for patients coming in complete remission (CR) and had undergone every 6 months in the first 2 years.

FDG PET/CT images were interpreted by two experienced nuclear medicine physicians who had access to the results of previous imaging and clinical information, but were unaware of the clinical results at the time of the post-therapy PET evaluation in order to avoid any significant influence on image evaluation.

A suspected relapse was defined as relapse proceeded by signs, symptoms or other clinical features such as rising serum LDH or suspected relapse using CT or MRI. **Asymptomatic relapse** was defined as relapse detected without any of the above features, on the basis of PET/CT imaging findings.

Qualitative PET/CT Deauville Criteria:

Deauville criteria are classified into 5-point scale. The five-point scale is now applied to both interim and end-of-treatment FDG PET/CT response assessment. Four categories of response have been outlined by the European Organization for Research and Treatment of Cancer (EORTC) where complete metabolic response (CMR) corresponds to score of 1, 2, or 3 [(2)].

Quantitative PET/CT Assessment:

The maximum standardized uptake values (SUV max) were recorded in case of Deauville criteria 3, 4 and 5 for the most active lesion in each patient 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. Another sizable ROI was drawn over the normal liver where

SUV max was computed using the following formula:

$$\text{SUVmax} = \frac{\text{maximum activity concentration in the neoplasm (kBq/mL)}}{\text{injected dose (MBq) /body weight (kg)}}$$

Total lesion glycolysis (TLG) was calculated in case of residual disease by multiplying the selected PET volume of total lesions (TMTV) as mentioned above by the SUV mean within that volume: **TLG = TMTV X SUV mean**

True positive (TP) results require either biopsy confirmation or diseases progression within 6 months of last report.

False positive (FP) results if proved not malignant by biopsy and clinical follow-up or, disease regression occurred without any treatment.

True negative (TN) results had no clinical relapse within the follow up period every 6 months up to 2 years.

False negative (FN) results manifest relapse within 6 months from the date of the last negative reporting scan after 2 years using clinical or radiological criteria.

Statistical Analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate.

Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5.

Accuracy was represented using the terms sensitivity, specificity, +ve predictive value, -ve predictive value, and overall accuracy.

P values less than 0.05 was considered statistically significant. Survival analysis was done using Kaplan Meier test to determine overall survival.

All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS:

Patients' characteristics:

This is a prospective study that includes 72 patients were histo-pathologically proven non-Hodgkin's lymphoma. All patients had clinical and complete metabolic remission as detected by PET/CT at the end of treatment. The study included 72 patients (37 males and 35 females) with median age 52 years. In the whole study group the highest incidence was 41% with DLBCL, 56.9% of patients were classified as stage IV. ***Table (1)*** showed the descriptive characteristics of the study group.

Table (1): Descriptive characteristics of 72 patients with NHL**.**

Clinical data	Number	Percentage (%)
Gender:		
Males	37	51.4%
Females	35	48.6%
Pathology:		
DLBCL	41	56.9%
Follicular	9	12.5%
T-cell rich B-cell	2	2.8%
Mantle cell	5	6.9%
Others	15	20.8%
Clinical stage:		
I & II	17	23.3%
III & IV	55	76.7%

Clinical characteristics of 72 patients with NHL:

IPI index was high in 28 out of 41 DLBCL patients (68.5%) followed by intermediate IPI index in 10 patients (26%) and only 3 patients showed low IPI index (4.1%). Forty five patients were presented with only nodal disease (62.5%), 10 patients showed extra nodal disease (13%) while 17 patients showed nodal and extra nodal disease at the time of presentation (23%). Main line of therapy was RCHOP in 48 patients (68.7%), RCHOP and radiotherapy in 15 patients (20.8%). ***Table (2)*** showed the clinical characteristics of the study group.

Table (2): Clinical characteristics of 72 patients with NHL.

Clinical data	Number	Percentage (%)
IPI index (DLBCL):		
High	28	68.5%
Intermediate	10	26%
Low	3	4.1%
Site of disease:		
Nodal	45	62%
Extra-nodal	10	13%
Both	17	23%
Treatment:		
RCHOP	48	66.7%
RCHOP + Rth	15	20.8%
Other treatment	9	12.5%

Follow up of the whole NHL study group:

During follow up of the 72 patients for a period of 24 months, the mean period of relapse was found at 9.5 months. 30 patients were in complete remission (41.7%), whereas 37 patients had relapse (51.4%), and 5 patients had indeterminate relapse (6.9%) according to clinical and PET/CT criteria.

These 5 patients showed indeterminate relapse with Deauville criteria 2 and 3 in PET/CT had no treatment with evidence of regression within 9.6 months of follow up. These 5 patients were added to the negative group. All the 30 patients with complete remission according to clinical and PET/CT criteria were still free of disease during follow up period. The other 37 patients had relapsed disease.

Thirty seven patients showed relapse during follow up period up to 2 years. The group included 18 males (48.6%) and 19 females (51.4%) with mean age of 47.6 years. Thirty patients showed remission during follow up period up to 2 years. The group included 19 males (51.3%) and 16 females (45.7%) with mean age of 47.6 years.

DLBCL was the most common histopathological types in groups, 26 patients (70.3%), in relapsing group and 15 patients (42.9%) in the remission group with statistical significant difference (P = 0.002) **(Table 3).**

IPI index in DLBCL (41 patients) with high grade were found in 17 patients in relapsed group (69.2%), while low grade was more common in 10 patients (75%) with significant difference ($p< 0.05$).

Stage III & IV were more common in relapsing group in 29 patients (78.4%). Whereas, only 12 patients (34.3%) were seen in the remission groups with no statistical significant difference.

Nodal diseases were common in both groups with no statistical significant difference as shown in ***Table 3***.

Post-surveillance follow up of the relapsed 37 NHL at the end of the study:

Further follow up at the end of our study, showed 12 patients (32.4%) reached a further regressive course with complete remission, 13 patients (35.1%) showed progressive disease, 4 patients (10.8%) died and 8 patients (21.6%) lost follow up. Figure 1 (a and b) showed NLH with lesion in mediastinum and lung and follow-up of the same case showed more progression of the lung lesions.

Deauville criteria for the relapsed 37 patients with NHL during their surveillance PET/CT scans. Deauville score at the time of relapse showed 11 patients were presenting with Deauville 4 (29.7%) and the remaining 26 patients showed Deauville 5 score (70.3%).

Table (3): Comparison of clinical parameters between 37 relapsed patients and 35 patients in remission with NHL.

Clinical data	Relapse 37	Percentage (%)	Remission 35	Percentage (%)	P value
Gender **Males** **Females**	 18 19	 48.6% 54.2%	 19 16	 51.3% 45.7%	0.226
Mean Age (years)	47.6		52		0.450
Pathology **DLBCL** **Others Types**	 26 11	 70.3% 29.7%	 15 20	 42.9% 57.1%	**0.002**
IPI index (DLBCL) 41 patients **Low** **Intermediate** **High**	 3 5 18	 11.6 19.2 69.2	 10 5 0	 75 % 25 % 0%	0.585
Clinical stage **I & II** **III & IV**	 8 29	 21.6% 78.4%	 23 12	 65.7% 34.3%	0.339
Site of disease **Nodal** **Extra-nodal** **Both**	 25 4 8	 67.6% 10.8% 21.6%	 20 6 9	 57.1% 17.1% 25.7%	0.619

Semi-quantitative metabolic parameters for the relapsing NHL group: Time interval for NHL clinical relapse to occur showed 71.4% sensitivity, 73% specificity, cut-off value of 9.5 months, area under the curve (AUC) is 0.714, 95% confidence interval (CI) 0.5-0.8 and P<0.006. **SUV max** was measured at the time of relapse for the 37 patients, which showed mean value of 9.5 with range 2.1 - 21 and SD ± 5.3. SUV max of the most active lesion after the end of therapy PET/CT and at relapse PET/CT showed ***statistical significance*** with the patients' outcome with ***P values 0.04 and P<0.008*** respectively. **TLG** at the time of relapse ranged from 7-456 with mean value of 116.65. TLG score at the end of therapy PET/CT did not show a statistical significance, but it showed a significant relation at relapsed PET/CT with ***P<0.001. (Table 4).***

Table (4): showing different diagnostic parameters of significant semi-quantitative variables using ROC curve analysis.

Parameter	Sensitivity	Specificity	Cut off Value	AUC	CI	P Value
Time interval for clinical relapse	71.4	73%	9.5	0.714	0.5-0.8	P<0.006
SUV max at end of therapy PET/CT	30%	83.3%	2.6	0.546	0.4-0.6	P<0.05
SUV max of relapse PET/CT	96.7%	29%	3.2	0.981	0.95-1	P<0.05
TLG of relapse PET/CT (g)	96.7%	82.9%	12.7	0.987	0.968-1	P<0.001

Diagnostic surveillance PET/CT for early relapse detection in asymptomatic patients showed sensitivity 70.27%, specificity 11.43%, positive predictive value 45.6%, negative predictive value 26.6% and accuracy 41.6%.Diagnostic surveillance PET/CT for early relapse detection in symptomatic patients detected by clinical or ***other diagnostic imaging using CT or MRI*** showed sensitivity of 97.3%, specificity of 85.7%, positive predictive value of 87.8%, negative predictive value of 96.7%, and accuracy of 91.6% ***(Table 5)***.

Table (5): surveillance PET/CT for early NHL relapse detection in asymptomatic patients and symptomatic patients

	Sensitivity	Specificity	PPV	NPV	Accuracy
PET/CT in Asymptomatic patients	70.27%	11.43%	45.6%	26.6%	41.6%
PET/CT in symptomatic patients	97.3%	85.7%	87.8%	96.7%	91.67%

PPV *Positive predictive value,* ***NPV*** *negative predictive value,* ***TP*** *True Positive,* ***TN*** *True Negative,* ***FP*** *False Positive,* ***FN*** *False Negative.*

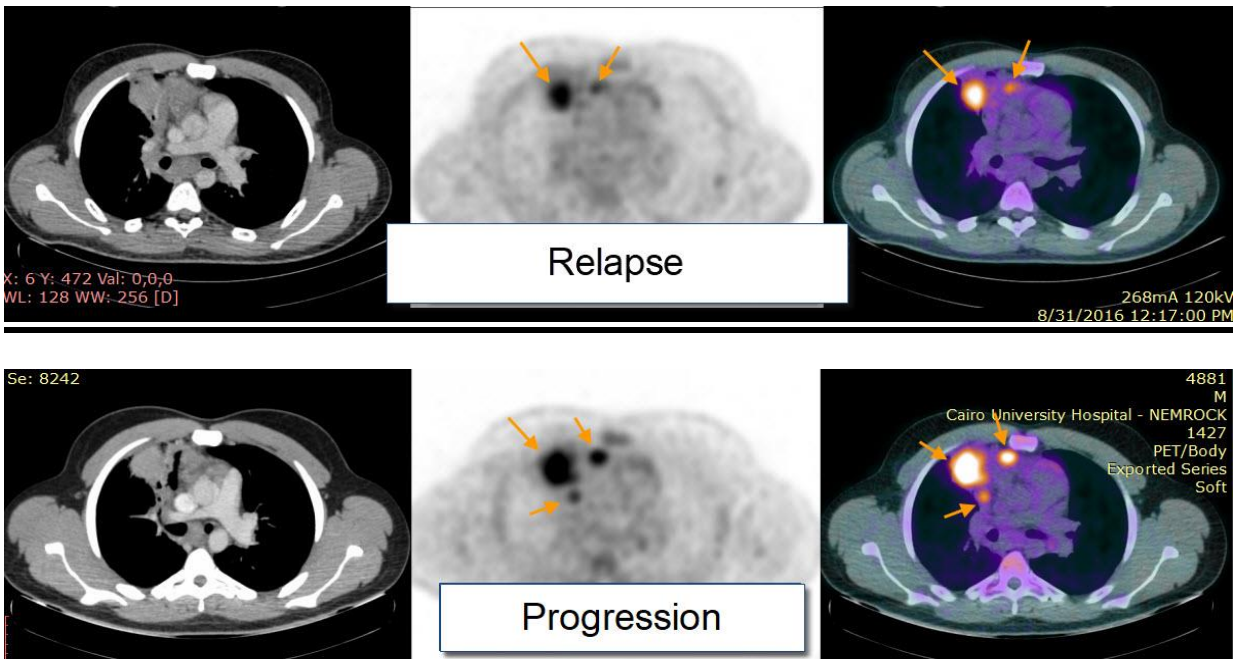

Figure 1 (A): 23 year old male with mantle cell lymphoma with stage III with relapse involving anterior mediastinum and pulmonary lesions together with inactive sub-carinal LN as seen in PET/CT scans.

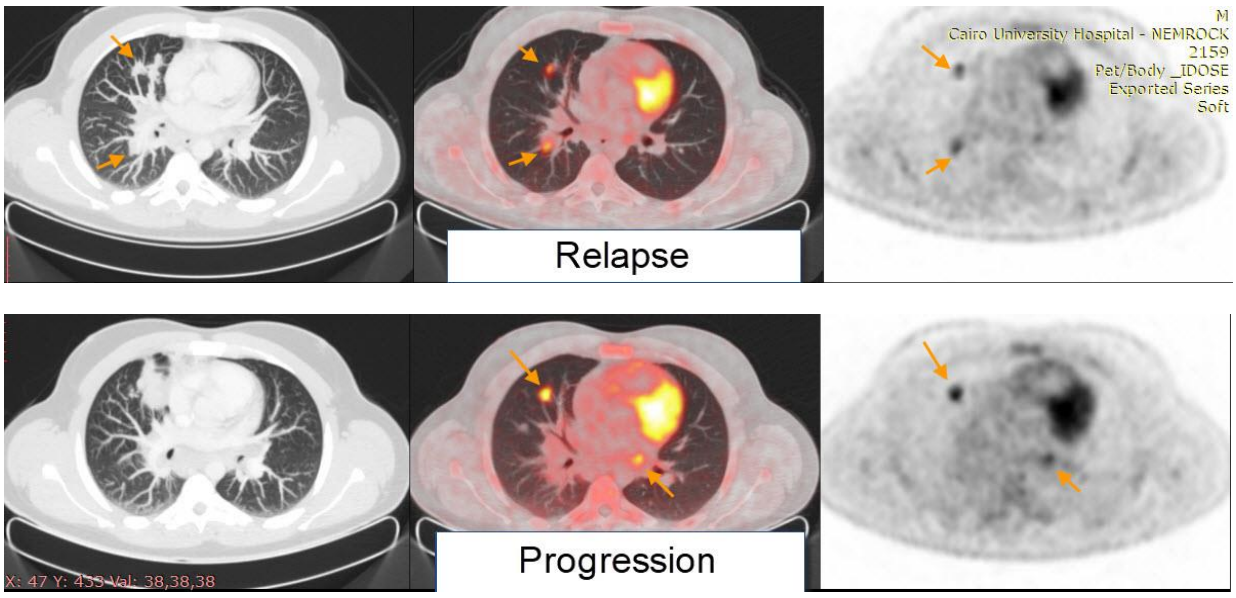

Figure 1 (B): The same patient with disease progression as PET/CT show increased FDG uptake involving right sided pulmonary lesions within the medial segment of the middle lobe and another lesion at the right hilar region. Lower row images show progressive increase in size and FDG uptake, however with imperceptible in right hilar LN.

Survival Analysis:

The overall survival was analyzed using Kaplan Meier test according to the outcome of the entire group of patients included in the study for 2 years and that was 84.7%, for remission group, while it was 67% for the relapsed NHL group ***(Figure 2).***

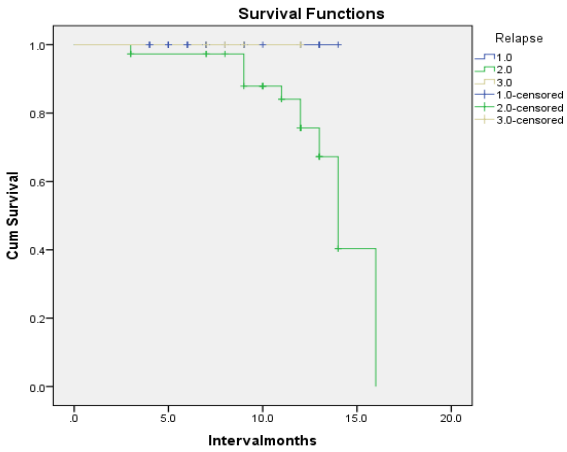

Figure 2: Overall survival curve for the whole NHL study group within 3 years**.**

DISCUSSION:

Response in lymphomas was previously assessed according to the International Workshop Criteria based mainly on morphologic criteria, with a reduction in tumor size on CT being the most important factor. However, CT usually showed residual masses as it is difficult to assess whether this represents viable lymphoma or fibrotic scar tissue. On the basis of these findings, the International Harmonization Project has developed new recommendations for response criteria for malignant lymphomas, incorporating FDG-PET into the definitions of response in FDG-avid lymphomas [(3)].

Several groups have reviewed the appropriateness of routine surveillance in HL and DLBCL, including the American Society of Hematology Choosing Wisely Campaign, which recommended against routine surveillance imaging for curable lymphomas due to concerns about a high rate of false-positive scans and an unclear survival benefit [(4)].

The aim of our study was to evaluate the role of 18F-fluorodeoxyglucose (FDG) PET/CT scans in the surveillance of patients achieving complete response (CR) after primary therapy for non-Hodgkin's disease, to assess the diagnostic accuracy of early detection of relapse and define a strategy for surveillance imaging.

Our study included 72 NHL patients with clinical and complete metabolic remission as detected by PET/CT at the end of treatment.

All patients underwent clinical and PET/CT imaging during regular follow ups at Nuclear Medicine unit, every 6 months for 2 years after treatment. In whole study group, the highest incidence was 41% with DLBCL and the second rank 9% with follicular lymphoma.

Whereas in ***Goldschmidt's*** study, the vast majority (97.6%) had DLBCL, one (1.2%) had peripheral T-cell lymphoma and one (1.2%) had lymphoblastic lymphoma. This discrepancy is mostly contributed to that we involved both aggressive and indolent lymphomas in our study.

But, ***Goldschmidt et. al*** only addressed aggressive NHL patients [(5)].

29 out of 72 patients of the relapsed NHL group (40.2%) of our study were classified as stage III-IV, while Goldschmidt et al showed that advanced stage at diagnosis was present in 65% of the patients.

Our study aligned with that of ***Goldschmidt*** study as both studies showed a positive correlation in detection of relapse with P value ($P<0.001$ in our study and $P<0.05$ in Goldschmidt's study) [(5)].

According to the study done by ***Cheah et al***, 11 patients (84%) of the relapsing group was presented as stage III-IV [(6)].

Also, in the present study, 22 patients (78.4%) showed relapse in advanced stage.

We also assessed IPI index in DLBCL subtype and was classified as low, intermediate or high index. It was found that 18 patients (69.2%) had high IPI followed by intermediate IPI index in 10 patients (26%) and only 3 patients showed low IPI index (4.1%), however no statistical significance was found for relapse detection $P=0.585$.

In a serious of 680 patients of prospective study from the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma. IPI index was assessed with 242 patients with IPI (0-1) which was 36%, 186 patients with IPI 2 (27%), 168 patients with IPI 3 (25%) and 84 patients with high IPI (4-5) and it was 12% [(7)].

In comparison to our study 69.2% of the relapsed group was in the high IPI index with statistical significance difference.

Also, ***Cheah's*** study, reported high index of IPI in 8 patients (62%) of the relapsed group and showed a ***statistical significance P<0.02*** [(8)]. For the whole study group, 45 patients were presented with only nodal disease (62.5%), 10 patients showed extra-nodal disease (13%) while 17 patients showed nodal and extra-nodal disease at the time of presentation (23%).

Also, ***Petrausch et al*** reported that 37 patients (49.3%) of their study presented with extra-nodal disease and the other half showed only nodal disease [(9)].

For the relapsing group, At the time of presentation, two thirds of the patients (67.6%) were presented by nodal disease only, 4 patients had extra-nodal disease only (10.8%) and 8 patients were presented by both nodal and extra-nodal disease and that accounted for 21.6%.

In comparison to ***Cheah's*** study, they classified the patients if 2 or more extra-nodal sites were present and they stated that 54% of the relapsing group showed 2 or more extra-nodal sites with significant P value 0.02 [(8)]. The discrepancy with our study could be attributed to variable number of patients in the study groups.

In the present study, during follow up of the 72 patients for 24 months with a mean period of follow up of 9.5 months, 30 patients were in complete remission (41.7%), whereas 37 had relapse (51.4%), and 5 patients had indeterminate relapse (6.9%) according to clinical and PET/CT criteria. These 5 patients ended in metabolic regressive course using PET/CT follow up and were added to the negative group.

Whereas in ***Cheah's*** study, Two-thirds of relapses occurred within 18 months of completing chemotherapy and 85% within 2 years, with a median time to relapse of 12.8 months, 13 patients (11%) had relapsed and 97 (84%) remained relapse-free in ongoing complete remission and seven indeterminate scans (5%), six of them were shown by follow-up to be negative for lymphoma and one was biopsy confirmed to be positive [(8)].

In the present work, relapse occurred in 26 patients (70.3%) were presenting with newly developed lesions, and 11 patients (29.7%) the relapse occurred in the same site of disease which was a significant parameter to relapse detection (P<0.001).

Similarly in ***Cheah's*** study, five patients (71%) had suspected relapses occurred at sites, which were previously uninvolved by DLBCL which was consistent with our results [(8)].

The present study revealed that evidence of true relapse was proved by close follow up for a period of 24 months. Suspicious relapse in further imaging by diagnostic CT scan or MRI scan or follow up PET/CT.

20 patients (54.1%) were proved positive for relapse by follow up by PET/CT which showed further progressive disease. 9 patients (24.3%) had progressive disease which was proved by biopsy. 4 patients (10.8%) have undergone conventional imaging CT or MRI with suspicious disease before referral for PET/CT.

In comparison to ***Thompson et al***; of the 104 evaluable relapse in 67 of the104 patients (64%) were evaluated for disease before their next scheduled follow-up visit; the other 37 relapses (36%) were detected at a scheduled follow-up visit; 22 were detected via CT (59.4%), 13 were detected via PET (35%), and two (5.4%) were detected by physical examination or clinical features which prompted a PET/CT scan [(7)].

At the end of 24 months of our study, 35 patients who were in remission remained relapse-free in ongoing complete remission. Regarding the 37 relapsed patients; after administering their second line of chemotherapy, it was found that 12 patients (32.4%) reached a further regressive course with complete remission after second line of chemotherapy, 13 patients (35.1%) showed progressive disease, 4 patients (10.8%) died from other causes and 8 patients (21.6%) lost follow up with no statistical significant difference.

Also, ***in Cheah's*** study, they reported eight died from progressive disease (61.5%) and five were in remission after second line of chemotherapy (38.4%). Six patients died from other causes [(8)].

In the present work, at the end of the primary line of treatment in complete remission status our results were as follows: 28 patients had Deauville 1 (75.7%), 4 patients had Deauville 2 (10.8%) and 5 patients had Deauville 3 (13.5%).

Whereas, Deauville score at the time of relapse showed 11 patients were presenting with Deauville 4 (29.7%) and the remaining 26 patients showed Deauville 5 score (70.3%).

We studied correlation of SUV max after the end of therapy and that measured during subsequent follow up scans of the 37 relapsed patients. They both showed statistically moderate correlation with the patient's outcome. The cut off value of SUV max of the most active lesion after the end of therapy PET/CT that could detect relapse was 2.6, with 30% sensitivity, 83.3% specificity with r correlation of 0.54 %. While the SUV max cut off value of the relapsed PET/CT was 3.2, with 96.7% sensitivity, 29% specificity and r correlation of 0.98. However, this is the first study to evaluate metabolic parameters using ROC curve analysis to determine the cut off value for relapse detection.

Zinzani et al., assessed role of PET/CT in the follow-up of lymphoma, they measured SUV max for patients who relapsed versus those who stayed in remission in 138 patients with aggressive non-Hodgkin's lymphoma. Their results were very close to our study results where SUV max among patients who presented with relapse compared with patients who stayed in remission was: median of 6.80g/mL (range, 3.5 to 29.0g/mL) versus median of 2.60g/mL (range, 1.3 to 3.2g/mL), respectively **(10)**.

Watabi et al reported a study on 20 patients with malignant lymphoma, to evaluate response to therapy with total lesion glycolysis (TLG) compared to peak standardized uptake value normalized for lean body mass (SUL peak) of the single target lesion [11]. In complete remission cases by TLG (n=14), 43% of them represented partial response by SUL peak, which had faint to moderate FDG uptake below the threshold of TLG. Six patients had relapse in the follow up period (637±378 days). Half of them were stable disease by TLG and the other half were complete remission by TLG and partial response by SUL peak. Area under curve of ROC analysis were 0.696 by TLG and 0.845 by SUL peak, which suggested SUL peak was more appropriate method for predicting relapse **(11)**.

In the present study, TLG measured at relapsed PET/CT during follow up PET/CT scans showed a significant relation with *P<0.001*. Its cut off value was 12.7, with high sensitivity 96.7%, 82.9% specificity and r correlation of 0.98.

Lugano classification discourages the use of routine PET/CT surveillance in the absence of a clinical indication and this recommendation has been incorporated into guidelines for management of DLBCL for patients with early-stage DLBCL, while the guidelines continue to allow CT every 6 months for the first 2 years after treatment for patients in complete remission (CR) [12, 13]. Whereas, the European Society of Medical Oncology guidelines, recommend the use of PET/CT in routine surveillance [(14)]. Our study showed the diagnostic accuracy of using surveillance PET/CT for early relapse detection in reference to ***other diagnostic methods*** (close follow up, biopsy or conventional imaging as CT or MRI) showed sensitivity 97.3%, specificity 85.7%, positive predictive value (PPV) 87.8%, negative predictive value (NPV) 96.7% and accuracy 91.6%.

Also ***Cheah's*** study results showed there were 13 TP scans (2.8%), six FP (1.3%), no FN and 424 TN (94.2%). The PPV was 68% and the NPV 100%. Of the seven indeterminate scans, six were shown by follow-up to be negative for lymphoma and one was biopsy confirmed to be positive.

If they include of indeterminate scans by scoring the former as FP and the latter as FN, respectively, test performance remained robust with revised sensitivity 95%, specificity 97%, PPV 60% and NPV 99% which is aligned with our results [(8)].

We also addressed the diagnostic accuracy of using surveillance PET/CT for early relapse detection in reference to *clinical features*. For the relapsed group in our study; 26 patients (70.3%) complained of clinical symptoms suspicious for relapse before follow up PET/CT scan, while 11 patients (29.7%) did not complain of clinical manifestations suspicious for relapse. Such group of asymptomatic patients on follow PET/CT showed sensitivity 70.27%, specificity 11.43%, positive predictive value 45.6%, NPV 26.6%, accuracy 41.6%. Whereas, it showed higher value in symptomatic patients with sensitive 97.5 %, specificity 85.5 %, PPV of 87.5 % and NPV of 96.7 % and accuracy of 91.6%.

Also, ***Thompson et al*** reported outcomes for cohorts from Mayo Clinic and Lyon, France to describe use of surveillance PET/CT or CT in DLBCL patients and for whom surveillance-related follow-up was available. Relapsed DLBCL was detected by surveillance imaging prior to clinical manifestations in 9 of 552 Mayo patients (1.6%) and 4 of 222 Lyon patients (1.8%) [(7)].

Additional cohorts by ***Cheah et al*** including 116 patients who underwent 450 PET/CTs and found that only 13 patients in CR relapsed and only 6 had relapse identified by scan without other clinical symptoms (1.3%) [8].

The PPV was 56% in patients with an IPI score <3, compared with 80% in patients with an IPI ≥ 3.

Whereas ***Avivi et al*** reported outcomes for 119 patients with DLBCL who underwent PET/CT surveillance [15]. In a subset of patients who receive R-CHOP, the PPV was 23%, with a false-positive rate of 77%. In comparison to our study, PPV was 45.6% and FP was 43%.

On the contrary, ***Zinzani et al*** performed a large prospective study of surveillance imaging for aggressive NHL (n = 183). In this study, patients underwent serial PET at pre-specified time points after achieving CR following first-line therapy. There were an increased number of relapses confirmed by PET (31%) compared with clinical signs alone (22%). The rate of true positive PET was highest in the first 18 months of follow-up [10].

El-Galaly and colleagues reported outcomes for 258 patients, including 173 with DLBCL, who had relapsing lymphoma and assessed their method of relapse detection and clinical outcomes. Twenty-six percent of patients with relapsed DLBCL had relapse detected by routine imaging compared with 41% with abnormal symptoms and 24% with abnormal symptoms plus abnormal laboratories/physical exam [16].

Furthermore, ***Avivi et al*** made a large prospective study evaluating statistical performance of surveillance PET in 183 subjects with aggressive NHLs, reported an extremely low FP rate of 1% only [15]. This low incidence is likely to be attributed to different criteria employed to define a FP test in this particular study, where a scan demonstrating an "unexplained, non-physiological uptake," was defined at the time of performance as an "inconclusive test" and was not included in calculations of FP rate [15].

The overall survival of 24 months was analyzed according to the outcome of the entire group of patients included in the study for 2 years and that was 84.7%, while for the relapsed group was 67%. These data suggest little utility for performing routine imaging in the manner currently employed in follow-up of NHL patients in CR.

Because relapsed aggressive NHL is potentially curable and can benefit from better outcomes with earlier detection of relapse.

Limitations of the study:

Our study has a relatively small sample size. Despite a standard systematic strategy to obtain patient and disease information there is some missing laboratory data. However, clinical diagnosis was depending on laboratory and diagnostic CT without including PET/CT imaging in initial staging.

CONCLUSIONS:

The current study shows that routine surveillance imaging with PET/CT in mandatory in asymptomatic patients with NHL in CR for detection of early relapse, while it is not beneficial in asymptomatic patients. Both metabolic parameters including SUV and TLC were valuable during follow up for detection of early relapse.

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